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STRESSES AND STRAINS OF HOMEOSTASIS.*

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The extraordinarily unstable stuff of which our bodies are constituted is persistently subjected to various external and internal conditions which, if not resisted, would profoundly alter its ability to function. Environmental temperatures extending from arctic cold to torrid heat, atmospheres ranging from the tenuous air of high mountain tops to the heavy and perilous murk of deep mines, sudden outputs of acid by the muscles as a consequence of strenuous labor, the losses of water and food reserves in thirst and starvation—all these contingencies occur to human beings in the natural course of experience, and though these hazards might well be expected to be damaging or fatal, ordinarily they are not; indeed, they may not prove to be even dangerous.

How does it happen that we can be so remarkably safe from these accidents of existence? The answer to that question is found in an admirable feature of the organization of our bodies—the arrangement whereby all our living parts, both the gross and the minute, are intimately in contact with fluid, as if immersed in it—the rapidly flowing blood and the more slowly moving lymph. Everywhere inside the lifeless layer of skin which covers us, the organs and tissues are set in a *fluid matrix*. If we make a small opening in the skin, at once the fluid begins to exude or flow away. This "internal environment," as Claude Bernard called it, has developed as organ-

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isms have developed; and with it there have been evolved remarkable physiologic devices which operate to keep it constant. Though the world outside us may be distressingly cold, though the heat and acid which arise from our own strenuous exertions may tend to become an overwhelming menace, we are not greatly disturbed, for our living parts touch only the body fluids which are maintained in an even and steady state. So long as this personal, individual sack of salty water, in which each one of us lives and moves and has his being, is protected from change, we are freed from serious peril. Because that protection is afforded by special physiologic agencies, I have suggested that the stable state of the fluid matrix be given the name *homeostasis*.

We shall gain insight into the ways in which homeostasis is maintained if we consider for a few moments two general relations of the nervous system. In one relation, through its receptors (or sense organs) and through its control of skeletal muscles which move the bony levers of the body, the spinal cord and brain are concerned with the external environment. Thus we learn, and thus we move from place to place and strive to alter the world about us as we wish. In the other relation, through connections with internal organs—with the heart, the bloodvessels, the gastro-intestinal canal, the liver and other viscera—*via* the autonomic nervous system, the spinal cord and brain are concerned especially with the internal environment. The autonomic system, as is well known, has three parts, the cranial, the sacral, and the thoraco-lumbar or sympathetic divisions. The sympathetic division discharges nerve impulses which accelerate the heart and contract or relax bloodvessels; which dilate bronchioles, set free sugar from stores in the liver, cause erection of hairs; and which stop the special functions of the digestive tract, discharge adrenin from the adrenal glands, and produce still other effects. Since the discharged adrenin is carried everywhere in the body by the blood, and since it has the same effects on the internal organs as the sympathetic impulses, the coöperation of the two agents may be regarded as constituting a sympatho-adrenal mechanism.

It is a point of considerable importance that the sympatho-adrenal system, when strongly excited, appears to act as a unit. No matter what the stimulus, the effect is diffuse and extends throughout the body. The arrangement of nerve connections with sympathetic ganglia favors that sort of effect[1] and the indiscriminate distribution of adrenin by the blood stream supports it. This tendency of the sympatho-adrenal system to act as a whole explains the occasional appearance of inappropriate features in the total complex of the reaction, *e. g.*, "gooseflesh" or the erection of hairs in fever and the increase of blood sugar during asphyxial states. In other circumstances these are useful features of the reaction, as when the hairs are erected in cold surroundings and sugar is dis-

charged from the liver if the glycemic level falls. The significance of this integrated response to a variety of stimuli will become evident later.

For the present I wish to try to make clear that it is the peculiar function of the sympatho-adrenal mechanism to preserve and assure a homeostatic condition in the internal environment. In doing so I shall offer a few illustrations.

When a normal warm-blooded animal is exposed to a cold atmosphere heat begins to be lost from the body to the cooler surroundings, and therefore the temperature of the internal environment might fall. If the animal is provided with hairs or feathers, however, they are erected in such manner as to enmesh a protective layer of poorly conducting air about the body and thus hinder the passage of heat outward. Also the surface bloodvessels are contracted, with the result that the warm blood from the interior of the body is less exposed to cooling. And furthermore, adrenin is secreted, and that acts to speed up the burning processes in the organism and thereby to produce more heat. Thus heat conservation and extra heat production are favored, which serve to keep the temperature even. Because of these arrangements for stable bodily temperature, warm-blooded animals are liberated from the limitations imposed during the winter season on cold-blooded animals, which are condemned to hibernate in sluggish inactivity. The erection of hairs, the contraction of surface vessels, and the secretion of adrenin are all consequences of action of the sympatho-adrenal apparatus. If the sympathetic division of the autonomic system is removed surgically, the animals thus operated upon become obviously defective when exposed to cold. There is no adaptive check on heat loss from the body because hairs cannot be erected, nor can surface vessels be constricted. Also heat production cannot be accelerated by adrenin because the nerves evoking that remarkable hormone are absent. The behavior of sympathectomized animals in cold weather is in accord with this lack of physiologic efficiency. During the winter they live almost continuously in the neighborhood of sources of heat. If placed in a cold room, so cold that water nearly freezes, we have found[2] that they undergo a rapid drop of bodily temperature—sometimes as much as 4° or 5° F.—which occurs although there may be vigorous shivering. Indeed, shivering—which is, of course, muscular activity accompanied (like all such activity) by heat production—is the only resource except exercise that is left to prevent sympathectomized animals from suffering a serious fall of body temperature. Note that the feature which is lacking in such endangered animals is the service of the sympatho-adrenal mechanism.

Another external condition to which organisms may be subjected is that of a lessened oxygen supply. Mountain climbers, and aviators who fly at great altitude, have to make adjustments to that circumstance, because the higher they go, the lower is the oxygen

pressure and therefore the smaller is the oxygen load which the red blood corpuscles carry away from the lungs to the remote cells of the organism. The problem is that of getting enough oxygen to burn the non-volatile acid which is constantly being produced by these cells. Should the blood, which is mildly alkaline, become acid, even to a slight degree, coma supervenes, and often death. If oxygen is adequately supplied, however, the non-volatile acid is burned to volatile carbonic acid and, since that is readily breathed away, the hazards of a severe acidosis are obviated. Clearly the way of avoidance of those hazards is through an adequate oxygen delivery to the tissues, where non-volatile acid is being made. Adjustments which work toward that end occur in the heart, blood-vessels and spleen. The heart is made to beat more rapidly and the bloodvessels are constricted in certain parts of the body, with the consequence that arterial blood pressure is raised; and under the higher head of arterial pressure the flow of blood is more rapid, *i. e.*, the number of trips made by the corpuscular carriers of oxygen from lungs to active tissues is increased. And, as a matter of special importance, the brain, which is peculiarly sensitive to lack of oxygen, and the heart, which needs oxygen continuously because it must be continuously active, are assured most favorable conditions because their bloodvessels are either not narrowed or are actually enlarged. Simultaneously, by contraction of the spleen, extra corpuscles are forced from storage in that organ out into the general circulation. Thereby, not only are the corpuscles more actively employed as conveyors of oxygen, but more corpuscles are called forth into active employment. Now the faster heart beat and the vascular constriction and the squeezing of the spleen are all results of sympatho-adrenal function. In sympathectomized animals, of course, these adjustments cannot take place. In our laboratory, in fact, Sawyer and Schlossberg[3] have found that whereas normal animals exposed to a low percentage of oxygen in the air (6%, for example) will endure the ordeal for at least an hour with no obvious indications of discomfort other than rapid breathing, sympathectomized animals faint and collapse in unconsciousness within a relatively short time—varying from 14 to 38 minutes. This sympatho-adrenal mechanism is clearly of the utmost value in keeping the fluid matrix from developing a dangerous acid reaction.

Not only does the sympatho-adrenal system protect against such perils as cold and low oxygen pressure, which affect the organism from the external world, it also protects against possible harm which might come from internal changes. A few illustrations will help to make that point clear.

Prolonged muscular activity—as, for example, cross-country running—uses the reserves of sugar in the body, and may actually empty the liver of its stored glycogen. The total amount of sugar in the blood at any time is little more than a teaspoonful, and yet

when great and powerful muscles are engaged in hard labor their requirements and the requirements of the nerve cells must be met from this scanty supply. The dose must be constantly renewed. For if the sugar level in the blood falls to approximately half the usual percentage, convulsions result; and if the reduction is not checked, coma and death follow. These facts were discovered by studying the phenomena which occur when the liver is removed and the organism is thereby deprived of its greatest sugar deposit.[4] They can be illustrated also by giving insulin, which, if present in excess, may gravely reduce the blood-sugar percentage. When, by an injection of insulin, the sugar concentration has been lowered about one-third of the usual percentage, a so-called "hypoglycemic reaction" appears, characterized by pallor, rapid pulse, dilated pupils, profuse sweating, and other effects, indicating that the sympatho-adrenal system is active. This system, as previously stated, is able to liberate sugar into the blood from the hepatic storehouse. And it may set free so much that, if the dose of insulin has not been overwhelming, the danger of convulsion is passed, and then the sympatho-adrenal system subsides into inactivity. The prime value of this arrangement can be readily shown in animals from which the sympathetic chains have been removed or in which the adrenal glands have been rendered inactive. Such animals have no effective means of increasing the blood sugar when it is reduced by insulin, and in consequence are extremely sensitive to the action of that substance. In studies of homeostatic regulation, Sawyer and Schlossberg[5] found that a dose of insulin which produces no noteworthy disturbance in normal animals occasions in sympathectomized animals marked symptoms, commonly attended by a convulsive attack and sometimes by collapse.

In considering the physiologic adaptations made when the oxygen pressure in the air is low, I mentioned incidentally the fact that some organs more than others in the body are affected by lack of oxygen. The brain, for instance, is much more sensitive to that condition than are the muscles; indeed, there are cells in the brain which are fatally injured if they are deprived of oxygen for even a few minutes, whereas smooth muscle can go without it for hours and still survive. The ever-active heart, also, has special need for a continuous oxygen delivery. The preservation of a relatively constant flow of blood to these essential organs is one of the most important homeostatic functions. It is assured by a fairly steady arterial blood pressure. When, because of reduced blood volume, the pressure is lowered to about 70 mm. of mercury, the supply of oxygen becomes insufficient for bodily requirements and then sensitive tissues begin to be injured. If, however, a sharp hemorrhage induces a drop of pressure to such a degree, a protective mechanism is brought into action, which, up to a certain point, is able to compensate for the lost blood by raising arterial pressure. Indeed, a considerable percentage of the

total blood volume may be removed and yet the pressure is soon restored to nearly its normal level. That this immediate effect is due to constriction of the bloodvessels, so that their capacity is made to fit the lessened quantity of their content, and is not due to an inflow of fluid from the tissues, is proved by noting that the blood is not diluted. It has long been known that the sympatho-adrenal apparatus is an important agent in this compensatory process. It is not only concerned with maintaining an effective head of pressure after hemorrhage—by reducing the size of the arteries and veins and speeding up the heart rate—but also it helps the situation further by contracting the spleen, as it does when the external oxygen supply is menaced, and thereby presses extra red corpuscles into service. A quantitative comparison of the ability of normal and sympathectomized animals to meet the test of hemorrhage, which was made by my collaborators, Schlossberg and Sawyer,[6] demonstrates vividly the essential rôle of the sympatho-adrenal mechanism in the critical state induced by a considerable bleeding. If the blood is removed in three or four steps, separated only by enough time to permit recovery of pressure, as much as 45% of the estimated blood volume can be removed before the compensating mechanism fails to be effective. In sympathectomized animals, on the other hand, the compensatory reaction to a single removal of 13 to 15% of the blood volume is in some instances strikingly absent and in other instances uselessly slight. Again we note the value of the sympatho-adrenal agency as a protector of homeostasis, homeostasis as a condition for the functioning of essential organs, the heart and the brain.

In the various examples of homeostatic adjustments which I have cited, certain internal or external conditions have been described which have tended to disturb the steady state of the fluid matrix; and the corrective processes have been indicated which have maintained the fluid matrix on its even course. We have seen that evidence points to the sympatho-adrenal system as the chief agency in resisting alterations of our internal environment, for when that system is not functioning the same stresses—cold, lack of oxygen, low blood sugar, loss of blood—which had no considerable influence on normal animals, became ominous for continued existence. In other words, sympathectomy changed the animals so that a stress which previously had been readily endured, afterward produced a breaking strain. It is clear, however, that by increasing the stress—by applying greater cold, by still further lowering the oxygen in the air, by reducing blood sugar to a greater degree, or by withdrawing more blood—the strain on the organism may become too great, even though the compensatory sympatho-adrenal apparatus is working to its utmost. Then the fluid matrix becomes altered. My colleague, R. G. Hoskins,[7] has suggested that it would be of interest and within the realm of possibility to

express the general "vitality" of an individual in terms of a "homeostatic index"—an expression which would state the measured ability to react, without disturbance of the fluid matrix, to a group of standard stresses which might readily disturb it. The chance of gaining insight into the strength and endurance of stabilizing factors of the organism, and thus into its ability to resist the operation of disturbing forces, makes it worth while to enquire where the limits lie beyond which stresses overwhelm these corrective factors and significantly alter the steady state of the internal environment. I have used the expression "significantly alter," because it is clear that in any case the signal for bringing the corrective factors into play is *some* alteration. Indeed, as Richet[8] long ago remarked, our bodies maintain their stability because they are variable! The point at which the stability is "significantly altered" should be defined. Perhaps, as a tentative definition, we may say that it is where the alteration becomes so great as to cause secondary, irrelevant effects and therefore lessens the efficiency of the organism. With that definition in mind, let us consider stresses which may place upon the protective agencies an excessive strain.

Before turning to conditions in the fully grown individual, it is well to recognize that the mechanisms which maintain uniformity in his fluid matrix are, in some respects, certainly not well developed in the newborn. There has been no need for them. The fetus is surrounded by a fluid external environment which does not differ greatly from the fluid internal environment. When born the baby is delivered precipitately from his liquid surroundings into surroundings which are utterly fresh and foreign. The new environment is gaseous instead of liquid; it is cold, it is noisy and brilliant and rough; a gasp fills the lungs with a thin, dry air and then water begins to be lost from the body with every breath. As Stanley Hall remarked, "At birth the child is cast like a shipwrecked mariner by angry waves on a strange and unknown coast and finds himself in a new and rigorous climate." Profound readjustments must be made, and they take time. With respect to temperature control, for example, the human infant is much less stably organized than is the adult. Not only do infants have a larger relative surface through which to lose heat to the outer world, but they are less quick and less effective in the reactions which preserve the normal state when the surrounding temperature varies. In consequence there may be sharp drops in the body temperature on exposure to moderate cold. In one case careful observations revealed that the rectal temperature during the early hours after birth varied from 95.4° to 98.6° F., the lowest point being reached after a bath in water at 102° when the room was at 71°.[9] Contrast this mild stress with that experienced in a cold bath, which may actually cause in the adult a slight rise of body temperature because of overcompensation.

Recent observations[10] have indicated also that the regulation of

blood sugar is not perfected in the newborn. The baby's blood-sugar content may be as low as 70 or 45 mg.%, and it oscillates from day to day and even from hour to hour much more than that of the adult.

The way in which these regulatory mechanisms become gradually more effective in keeping steady the conditions in the fluid matrix is not understood. Mere exercise of the stabilizing process may result in the stability of later years, or it may be a consequence of the natural processes of growth and development. The existence of some defects in infants, however, indicates that others may be present that have been overlooked. Is the water content of the blood preserved as well in childhood as in the full-grown? Is the calcium and phosphorus relation maintained evenly in the early years when rickets is likely to appear? These and many other questions which call for answer indicate that the development of various corrective controls of the internal environment presents a largely neglected field of research. We need information in that field in order to judge more fairly the status of the growing child and to predict more reasonably what may be expected as time passes.

In later years the homeostatic regulators, repeatedly exercised and put to test, have a high degree of efficiency. And yet there are limitations to their ability to preserve a steady state in the fluid matrix. And that ability may well vary under different general conditions, during the normal and pathologic ups and downs of existence in an ordinary life cycle. Information on many of these points is not yet at hand; indeed, one of the objects of this lecture is to indicate where more knowledge is needed. It will be pertinent, therefore, to survey some of the stresses of homeostasis to which we are not uncommonly subjected, in order to learn how well the organism meets them and how much strain is imposed.

Perhaps the best approach to the problem which is before us is by way of considering what happens when we engage in prolonged and vigorous physical struggle. In various ways it tends to disturb the constancy of the fluid matrix. First, such struggle is accompanied by a large output of heat from the laboring muscles. The extra heat, if allowed to accumulate in the blood, would raise the body temperature to a disastrous degree. By action of the sympatho-adrenal system, however, sweating is stimulated, and more blood is sent through surface vessels which are cooled by evaporation of the sweat, and thus extra heat is eliminated. Again, as we have seen, a lasting muscular effort uses blood sugar, and the danger of hypoglycemia is avoided by sympatho-adrenal mobilization of sugar from its seclusion in the liver. And furthermore, there is danger from the development of non-volatile acid metabolites, especially lactic acid, which, if not burned to volatile carbonic acid and eliminated, may cause a markedly defective functioning of the very muscles which are active. As we have noted, through the agency of the

sympatho-adrenal system the heart is accelerated, the arterial pressure is raised, the spleen is constricted, and the red blood corpuscles, augmented in numbers, are sent at a faster pace to perform their task of conveying the needed oxygen. Now, we may engage in such a degree of muscular exercise that heat and acid are produced, and sugar is used, without affecting to a noteworthy degree the usual steady state of the fluid matrix. Or the exercise may be such as to raise the body temperature, shift the reaction of the blood markedly in the acid direction, and reduce the sugar percentage to a low level. It is when the temperature is elevated, let us say a degree or two F.; or when the oxygen delivery is not sufficient to burn the lactic acid at the rate of its production so that a noteworthy "oxygen-debt" is induced; or when the blood sugar is brought below, say, 70 mg. % — in spite of the protective mechanisms working, in each instance, to oppose the change — that the stress might be regarded as becoming excessive or *critical*, *i. e.*, inducing a breaking strain in the homeostatic mechanisms.

Exercise is clearly too complex and awkward a method of measuring the critical stress. Exposure to a standard high temperature in an atmosphere of standard humidity until the heat regulatory mechanism fails and the body temperature rises to a standard extent; or giving a standard dose of insulin and noting whether and when it overwhelms the compensatory reactions and produces signs of hypoglycemia; or breathing air which has a standard low oxygen content until adjustments of the respiration and circulation prove inadequate and indefinite symptoms of oxygen want appear — such would be relatively simple ways of learning the critical stresses of these distorting factors. I have put the suggestions in tentative form because experience might alter the methods — indeed, probably *would* alter the methods, which could be applied in measuring the critical stresses.

When we consider the fundamental importance of constancy in the fluid matrix of the body — how elaborate the physiologic devices for protecting it, how serviceable it is in liberating us from being subjected to external and internal conditions which would be disastrous, and how widespread the damaging effects when the constancy fails — when we consider these matters, we see the value of finding a reliable method to determine how efficient the protective devices are. Such a method would not only test the responsiveness of the sympatho-adrenal system as a regulator of the internal environment, but would also indicate the ability of the organs which are called into action by that system to play their rôle in the regulatory process. And it might be especially valuable in giving us information regarding habits and practices which alter, favorably or unfavorably, the homeostatic mechanisms.

Unfortunately, no intentional effort seems to have been directed toward the invention of means of measuring the critical stress which

various conditions might place upon the regulators of homeostasis. I have already suggested (see p. 9) exposure to insulin hypoglycemia, humid heat and low oxygen tension as possible ways of discovering the limits of the homeostatic regulators. Of these, insulin hypoglycemia seems least likely to be useful. The test would probably vary greatly with the nutritive state of the subject; the secondary effects—sweating and hunger, for example—would be partly subjective and would require considerable time for their development; and the analyses of blood sugar would be rather complicated and slow. Exposure to humid heat might likewise be difficult, because a special room or chamber, capable of being warmed and moistened to a standard degree, is necessary in order to make the test accurate. Of the three methods which have been mentioned the breathing of air containing a measured low percentage of oxygen appears to be the most readily applied. Because the sympatho-adrenal mechanism, as previously noted, works as a unit when strongly stimulated, a variety of tests is not demanded—*one* which is *reliable* is sufficient. And already experience has proved the possibility of using anoxemia as a measure of the adaptive adjustments of the organism, with objective indicators of the secondary disturbance when the stress becomes too great. Perhaps the greatest advantage of this means of evaluating the effectiveness of the preservers of constancy lies in the nature of the secondary disturbances; they are effects on the central nervous system, and consist in lessened ability to perform certain routine tasks. Since no system in the body is so sensitive as the brain to lack of oxygen, the anoxemia test is associated with an extraordinarily delicate indicator of the critical stress.

In principle, two ways of employing a method might be used to assay homeostatic efficiency. First, a standard severe stress, slightly more than that commonly endured, could be applied, and a study then made of the time which passes before a critical strain is reached. We may call this the method of *fixed stress*. Or the stress could be gradually increased until a critical or breaking strain is revealed, when the degree of the stress could be measured. This would be the method of *variable stress*. By either way it would be important to note not only the action of the sympatho-adrenal system as a coördinating agency, but also the action of the effector organs by which that system performs its functions. Only thus would one obtain evidence of where the weakness lies.

It has been interesting to find that both phases of the method of testing homeostasis by lack of oxygen were applied by a group of investigators who, during the World War, were charged with the problem of devising means for determining the physical fitness of pilots and the conditions which affect the ability of pilots to fly at high altitudes. A "Manual of the Medical Research Laboratory"[11] reports in detail the two ways of testing. The subject

was placed in a chamber in which the oxygen pressure was set at a low level (the method of fixed stress), or he had to rebreathe a certain volume of air (from which the carbon dioxid was continuously absorbed) until the oxygen pressure was more or less reduced (the method of variable stress). The latter proved the simpler and the more commonly useful means of making the examination. The subject, as a rule, did not experience any discomfort; indeed, he was usually quite unaware that the low oxygen tension had produced any change in his physical state, although by his responses he may have shown remarkable secondary effects on his nervous system.

During the period of rebreathing the secondary effects were determined by observers who recorded carefully and frequently the respiration, the pulse rate, the systolic and diastolic arterial pressures, as well as the performance of set tasks which demanded close attention and coördinated voluntary acts. When the subject's diastolic pressure fell sharply, or his heart, which had been accelerating, began to beat more slowly, or he lost consciousness as revealed by total failure to pay attention to his tasks or by fainting, the rebreathing was stopped. By analysis of the air from which he had been taking oxygen it was possible to estimate the altitude equivalent to the oxygen percentage which had proved too low for his compensatory reactions. Thus, with 21% oxygen at the start (representing sea level), 14% left in the apparatus at the time of the "break" would represent an elevation of about 10,000 feet; 10%, about 20,000 feet; and 8%, about 25,000.

In their reactions to this test men were found to vary in one of two general directions—toward fainting or toward failure of task-performance without fainting.[12] The physiologic aspects of the reaction included practically always a large increase in respiration. Of course, that is in addition to adjustment of the sympatho-adrenal system, unless dilation of the bronchioles be admitted as a change which would render heavy breathing more economical. The striking sympatho-adrenal adaptations which occurred in those who adjusted well to the diminishing oxygen tension include a faster pulse rate and a rise of systolic pressure. Also there is evidence that the heart puts forth a larger volume per beat. These changes may be regarded as serviceable in providing a faster blood flow and consequently a greater oxygen delivery to the most essential organs of the body (and those most sensitive to oxygen want), the heart and the brain. In other words, the changes are directed toward assuring homeostasis for those organs, even though other less immediately important organs in the body might suffer. Fainting is imminent when diastolic pressure begins to fall rapidly, or there is a drop in systolic pressure, or the heart beat becomes slow. In these circumstances the lower brain centers, controlling the heart and bloodvessels, appear to be the more sensitive indicators of failure to receive an adequate oxygen supply. In the non-fainting class

the blood pressure and pulse may remain fairly satisfactory, in spite of a low oxygen percentage, but the subject becomes stupidly unaware of his surroundings and of his own lapses of attention. Here the cortical functions of the brain are first to signal the deficit in the oxygen supply.

It seems probable that a standard for judging a critical stress from anoxemia could be found that would not require the test to be carried so far as to be near the edge of fainting or loss of consciousness. In most of the published records which carry the psychologists' observations, there are signs that, well before the circulatory changes have developed, the subject has begun to manifest characteristic disturbances of cerebral functions—such as confusion, wavering attention, clumsiness, delay and error in making the required motor responses. It is said, furthermore, that the reactions studied by the psychologist are the "best criteria as to the efficiency of the compensation." In the Government Manual (p. 87) the statement occurs, "As our work has progressed we have become more and more impressed with the perfectly definite effects following exposures to altitudes below 5000 feet." If such effects could be proved characteristic, and indicative of too great a stress, *i. e.*, a stress so great that the compensatory mechanisms are beginning to fail—even though 5000 feet would have to be much surpassed—a practical and simple test might be devised which would yield valuable information regarding the influence of common experiences on general bodily condition.

I have presented a sketch of the method of testing aviators because it has definitely proved that the efficacy of the adjusting apparatus in control of the fluid matrix can actually be evaluated. Indeed, the aviation tests have not only brought out clearly the quality of different types of physiologic organization, but also have disclosed evidence that bodily efficiency varies in a remarkably interesting manner at different times. A few illustrations will give point to these statements.

In some instances the observers found that there was "complete inefficiency" when the oxygen deficit marked an altitude as low as 6000 feet. Such subjects were in the main constitutionally inferior —often undersize, with flat chests, clammy, mottled hands and poor complexion. In the same class were men near middle age who had led a sedentary life and were overweight and of flabby musculature. Any functional defect of heart or bloodvessels was, quite understandably, the occasion for a low score. As the Manual (p. 32) remarks, "There is a certain range of greater or less breadth through which the external factors of the environment may be varied and yet be met by an automatic adjustment of the physiologic processes in the body which will preserve the vital balance of the mechanism. But beyond a certain point, specific for each organism, changes in the external condition will necessitate more radical alterations which will tax the compensating mechanisms to the

utmost capacity in order to prevent disaster. Theoretically the organism which has been called upon repeatedly to make a certain kind of adjustment (in this case supplying oxygen to meet a need) will be the one most capable of responding when an extraordinary demand is made. . . . . Since physical exertion does increase the demand for oxygen it is to be expected that the organism which has been called upon to do physical work frequently will have acquired marked powers for compensating for oxygen want."

Although, as a rule, the athletic or physically fit person is best able to meet the exigencies of anoxemia, he himself may show noteworthy variations of response to low oxygen percentages, according to his "condition." Thus during a cold, or after a recent illness, or when the body has been damaged by unhygienic living, or weakened by inactivity or by worry or dissipation or loss of sleep, the capacity for endurance of oxygen deficiency is apt to be reduced. Then as the oxygen in the rebreathed air becomes less there is an earlier onset of inefficiency than would occur if the subject were quite fit. For example, one of the subjects, often tested and proved to be exceptionally hardy, was brought on a particular day to an oxygen level equivalent to an elevation of 22,000 feet, and was kept there for 15 minutes with hardly any effect on his general responsiveness. That evening he dined with friends, drank a moderate amount of alcohol, and went to bed late. The next morning he felt a little giddy and had a slight headache. Then, when tested at 18,000 feet, he became cyanotic and was wholly incapable of meeting the psychologic tests. Only by prompt administration of oxygen was he prevented from fainting.

It is hardly necessary to point out that this mode of estimating the capacity of the sympatho-adrenal apparatus (and its subservient organs) to meet certain standard requirements has given us quantitative information regarding "fitness," and regarding the circumstances which affect "fitness," that we have never before possessed. It is not necessary to use the vague phrases "being in good condition" or "being in poor condition," if a test can express graphically and in fairly accurate terms what those phrases mean. The possibility of securing that degree of exactness in a realm of medical observation where judgment has been uncertain and description indefinite would amply justify an effort to simplify the aviation tests so that they could be applied reliably to medical cases without too great expenditure of time. Or it is conceivable that some other ready way could be found for judging sympatho-adrenal efficiency. At this point I wish merely to emphasize the importance of establishing a satisfactory uncomplicated method of assaying that efficiency. If that could be done we should have a means of learning how all sorts of human experience affect the fundamental factors which determine homeostasis. A vast territory, enticing for biologic and medical exploration, would be disclosed. We should have to learn how steady are the steady states and where the critical

stress is found, not only in normal individuals, but also in individuals at various developmental epochs and during various disorders. Childhood, adolescence and old age, the exacting periods of puberty and the climacteric, prolonged labor, fatigue, the demands of school, the values of different sorts of training—all these and many other conditions (besides infection and insomnia, worry and dissipation, already mentioned) could be made to tell their influence on the agencies which maintain uniformity in the fluid matrix. Indeed, the whole gamut of human diseases might be studied from this point of view.

The main objectives which I have had in mind while preparing this lecture are two: I have wished to rouse interest in the stability of our internal environment and in the admirable regulatory mechanisms which maintain stability and which are found in the functioning of the sympatho-adrenal system; and I wished also to indicate the importance of a means of estimating the efficacy of that system as a regulator of bodily stabilization. Unfortunately I have not been able to bring to you an account of a well-tried method of discovering the critical stresses in homeostasis, a criterion for judging the degree of perfection of the corrective and preservative devices in our physiologic economy which assure us freedom for our more interesting and important activities. But am I right in saying "unfortunately"? Does not the chase often yield quite as much satisfaction as the quarry? Of our "more interesting and important activities" is not the quest for illuminating facts among the choicest and most admirable? Perhaps I had better say "fortunately" there is much significant and rewarding research ahead of us, research needed for the relief of man's estate. It would be most gratifying if any hints I may have offered would serve as a stimulus to fresh endeavors to bring us new knowledge and new power.

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THE RELATION OF DENTISTRY TO MEDICINE.*

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Dentistry, or stomatology, as some now prefer to call it, is gradually being given the standing of an important junior member of the medical family. While its interests have been largely concentrated, during its comparatively short life as an organized profession, in the field of mechanical and surgical therapy, of late it is being realized that many of its problems lie directly in the field of general medicine. Its course as a member of the medical family will be that of any other well-conducted junior—it will follow in the footsteps of its elders, at least such footsteps as have led forward, and it will continue, in its practice, in its education and in its research to be guided by the experience of those who have preceded it on this course of professional development.

My theme today—the relation of dentistry to medicine—is a phase of progress in the history of medical art and science. Dentistry is one of the subdivisions of the healing art and occupies in practice a relation to the main body of medicine essentially like that of otology, laryngology and ophthalmology. Like all these, it springs from the main trunk of general medical knowledge and experience.

Gradual Recognition of Teeth as Organs. The necessity for the ministrations which the dentist now gives is as old as the teeth themselves, just as—if we are to go back to origins—the necessity for the ophthalmologist was determined by the occurrence of the eye. But by one of the most singular aberrations of the human mind, extending over centuries, teeth were long regarded as if they were something extraneous to the body—something essentially inanimate presumably because of lack of a visible capacity to repair themselves. They were thought to be a sort of added convenience or mechanism—as though they were not produced by the body in which they occurred, but were added to it. Teeth had the rank and standing of mechanical appliances, existing largely for the purpose of mastication, with adornment also playing an important rôle. Had it not been for toothache, which brought poignant evidence that they were not inanimate, teeth never would have been forced upon our attention.

Dentists Admitted to Medical Ranks. Perhaps it was this anomalous status of the teeth which accounted for the no less anomalous status so long occupied by the dentist. Over extended periods he shared in the dubious classification of the barber-surgeon union.

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A later stage was that of the tooth-puller, when he was confused in the public mind with the traveling charlatan and the local jack-of-all-trades. For a century or more he lived in a no-man's land between a profession and a trade. Dentists, even in our own time, are being admitted very slowly and not without resistance, to the general company of physicians and surgeons. Within the lifetime of those present the dentist has continued to be regarded in some quarters as a mechanic and his occupation as a manual craft. It is not 6 months since a learned professor at my own university coupled dentistry and plumbing as the two leading contributions of America to culture. It is difficult for the dentist to feel adequately flattered by the collocation.

Undue Specialization. On the threshold of the medical profession the dentist meets a new danger from the undue specialization that has been attacking in epidemic proportions the entire healing art, separating it into formal divisions and breaking it up into a number of water-tight compartments.

Specialization was in its origin unavoidable. It was made necessary by the expansion of the field of knowledge. Since the death of Roger Bacon, in 1294, no one mind has been able to embrace the whole of science. Subdivisions and specialization were made necessary by the rapid and immense increase in nearly all fields of knowledge. As the aggregations of facts, accumulating at accelerated speed, piled up before the scientist, in quantities so vast that they swamped the mind, they led to increased specialization and resulted in many scientists becoming wholly immersed in minor subdivisions and specialties.

Our zeal for specialization in all directions has carried us to extremes. The banker has sometimes tried to conduct his affairs as if they formed a water-tight compartment and as if finance were independent of business. The physicist, the chemist, the economist have essayed to live within a tight fence where other specialists might not intrude. Medicine has broken its province into a score of principalities. Even the restricted field of dentistry has fallen into the current error; it has not merely set up its own boundaries, but has split its enclosure into subdivisions—prosthetics, orthodontia, periodontia, oral surgery, etc.

Medical Subdivision. In course of time the law has allotted to each its own portion of the body, and the mouth with its complement of teeth has become the legal domain of the dentist. The rest of the body remains as yet the domain of general medicine, but whether the various specialties of medicine will be content, whether they will not each demand its "pound of flesh," its segment of the body, to be its proper province, defined and apportioned to it by legal enactment—that is a question. It is no great feat of imagination to see the body all apportioned out and allocated, organ by organ, part by part, to the ophthalmologists, orthopedists,

laryngologists, cardiologists, gastro-enterologists, gynecologists, etc. How far would such division go? To what lengths would the jealousy of legal and medical rights carry our energetic specialists? One shrinks from the vision and wonders whether the ancient writ of *Habeas Corpus* would not have to be revised to read *Habeas Nares, Habeas Cordum, Habeas Pedem!*

No! Specialization will not go to such lengths; common sense will intervene. It is possible to make legal division of the body, but Nature knows none. Her consent has not been given. No legal barrier can stop the toxin from an infected tooth spreading to the heart and interfering in its action, or to the joints and stimulating arthritis, or to the eye and affecting vision, or prevent a dysfunctioning heart from affecting unfavorably other structures. All specialization, whether it affects dentistry and general medicine or as it affects the various subdivisions of both, can be justified, not as a means of separation, but only as it aids and facilitates coöperation.

The Status of Dentistry. Dentistry has marched, step by step, to a place where it must be regarded in general as belonging to medicine. The status cannot yet be regarded, however, as wholly satisfactory—neither on the side of professional practice, nor yet as regards professional education. This is partly due to the action of the medical authorities of another day in refusing to admit dental subjects to the medical curriculum. The consequence was the establishment of separate dental schools with their own curricula and separate professional organizations. It is undeniable that the independent course then taken by the dentists and their attitude of self-sufficiency accounted in some measure for a certain aloofness of manner on the part of the medical profession. Separate dental schools at any rate came into being, not usually on equal scientific and intellectual level with the medical schools of the same period, and sometimes on a level decidedly lower. With the passage of time this gap is in process of being closed. The requirements for admission at the better dental schools and the general requirements for the dental degree are not inferior to those for the medical degree. Nor is the dental student at graduation less well prepared, but, on the contrary, rather better than his medical confrère, for the immediate practical problems of practice.

Dental and Medical Students. In general, there is visible today a growing affinity of the curricula of dental and medical schools. In some dental schools the work of the first 2 years of the course is identical in subjects taken and not inferior in quality to that of the first 2 years of the medical course and is frequently taken in the same lecture rooms and under the same instructors. The routine of lecture, of study and of laboratory work, and the personal relations set up with fellow medical students and professors tend to establish

and maintain common standards, lifelong habits of thought and bonds of fellowship.

On the medical side also there are tendencies toward closer relations in the curriculum. At least one medical school has moved to establish within its regular course, requirements in the dental field similar to the requirements set up in ophthalmology, otology and laryngology. This will further broaden the common ground and will prepare the way for a common footing in hospital service when, as is inevitable, it becomes the general practice of hospitals to have dental interns. In at least 2 hospitals with which I am familiar this has already come about.

For a Uniform Curriculum. The relation to medicine will be more satisfactory when the requirements for entrance to the dental profession are more uniform and when all dental schools adopt and enforce the standard of the leaders. That condition is rapidly being brought about. (This desirable goal has been made more attainable by the aid of the Carnegie Corporation, enabling the American Association of Dental Schools to make a study of the dental curriculum with regard to the requirements of the profession. As the same requirements and standards are applied to dentistry as to other specialties of medicine we shall find the old *odium medicum* disappearing.)

Conversely, on the side of the medical schools, there is an approach to dental subjects which indicates a more sympathetic understanding, and it is a matter of congratulation, alike to the medical and the dental faculties, that medical students show a keen and decided interest in dental subjects—an interest extending to the point of requesting an increase in the number of sessions devoted to dental problems.

Dr. Thayer on Interdependence. This whole relationship has been a matter of serious interest to many of the best minds of the profession. For example, the late Dr. William S. Thayer, one of the most distinguished and beloved members of the profession of his generation, as inspiring a friend to many of you as he was to me, in a report on the Harvard Dental School wrote as follows:

"The ophthalmologist and the physician meet on common ground: they are members of the same medical societies. Their subjects are discussed at common meetings. The dentist and the physician do not meet on the same common ground. This is unfortunate for the physician, for the dentist and for the patient. The circumstance that the requirements for admission to dental schools have been lower, and the circumstance that the amount of general and medical education demanded of the dentist has been less than that demanded of the physician and surgeon, have worked to place the dentist at a disadvantage in the medical and general community. This has not only been a disadvantage to the dentist, it has been a

very real disadvantage to the medical profession. It is, we believe, of importance to medicine that the time may come when . . . dentistry will be, as it should be eventually, one of the specialties of surgery . . ." And he closes by saying: "As the years go by, the importance of that branch of surgery practised by the dentist becomes more and more evident, and the interdependence of dentistry and the other branches of the art of medicine and surgery clearer . . ."

Hospital Service. As has already been suggested, a further step of progress will be made when dentists are regularly to be found in our hospitals as residents and interns. Such a step is desirable in the interests of the general health, because hospitals are the true mixing and testing grounds for the various groups of practitioners and specialists, true medical melting pots.

Perhaps even more important is the development of dental diagnosticians—a forward step proposed by President Lowell, of Harvard, strongly advocated by him, and under serious consideration in some of our hospitals. No one who has had experience in ward walks can have failed to realize how valuable in some cases a dental diagnosis may be. Although the subject of the mouth as a primary focus of systemic disease has rather overshadowed other aspects of the whole problem, we are now beginning to realize that certain diseases display early symptoms in the mouth—to the extent that we may even call the mouth a barometer of body health. Certainly no case can be regarded as thoroughly studied until an accurate and complete survey of mouth and teeth has been made. If this be true, the more effective and closer the coöperation of dentist and physician becomes, the better will be the service rendered the patient.

In all the professional relations in which dentists and physicians meet, in classroom, hospital clinics, as well as the routine of practice, the relations tend to grow closer and the exchange more reciprocal and coöperative. This is because the basis of common interests, common knowledge and common training grows constantly broader and is better understood.

Research. Nowhere is this plainer, nowhere is coöperative exchange more fully taken for granted and more imperative than in the field of research. Every investigator learns early in his experience that research cannot be conducted on the water-tight compartment basis. It is constantly crossing lines of technical, departmental and professional knowledge, and as fast as it expands it draws men of different faculties and diverse sections of science into ever closer coöperation.

This inevitable interrelation is illustrated wherever research, whether it begins in the dental or the medical field, is being carried on. For example, in one of our dental schools considerable research

is being conducted in the three major fields of dental disease: caries, pyorrhea and malocclusion. The field of caries demands especial attention because it is the most universal and the most familiar of all human ailments of our day. It is also an ailment which brings in its train many *sequelæ* to which medical men must direct their attention. Caries, therefore, of necessity interests medical men.

Research on Caries. In the school to which I refer there are no fewer than 8 pieces of research being carried on upon different phases of caries. This is natural for the reason that, as everyone knows, there is a wide difference of opinion as to the cause of the ailment. Since the days of Miller, when there was general acceptance of the view that caries was a germ disease and that all we had to do was to find and isolate the bacillus, we have gone through a series of changes of opinion. While some are still pursuing the bacteriologic trail, others have become equally convinced that the cause lies in nutrition. Within the field of diet again we have a number of more or less conflicting theories.

Interrelation in Research. No matter what theory the investigator in this subject of dental caries adopts, he will find that his work will carry him immediately across the lines of the established fields of medicine. For example, the study of the vitamin and mineral deficiencies will bring him immediately into close relations with active workers in several fields of research and, particularly if he is wise and fortunate, into cordial collaboration with the men who work in biochemistry. Again, as soon as he begins to study the effects of caries upon dental tissues, he will find himself in the field of pathology and coöperating with men in the pathologic department of the medical school. Let him turn to the effects of the Bacillus acidophilus, and he is at one step in the field of the bacteriologist and is again in close coöperation with the bacteriologic division of his medical school.

If he has gone further afield, and has become attracted by the effects of the endocrine glands as predisposing to caries, he will not advance far without being in coöperative relations with the men similarly engaged in the department of anatomy or surgery.

It is plain, therefore, that even within this single field of research into our most commonplace ailment, caries, we shall be involved in all four of the major departments of medicine and shall come, if we are fortunate, into happy coöperation with the men doing similar work in the departments of pathology, bacteriology, anatomy and biochemistry.

Interrelations in the Study of Malocclusion. The other divisions in which dental research is being carried on—certainly in one school, and I think perhaps in many others—lead equally to the same result, that is, to the impossibility of any effective research which

does not cross the boundaries of some, if not all, of the major divisions of medicine, and does not involve interrelations of the closest kind if effective work is to be done. For example, take the work which has been continued for some years by one of my colleagues in malocclusion, which leads directly to the study of bone growth. Ingenious forms of investigation in this field have led to the use of madder to reveal the modes of growth in bone, especially under various forms of strain. Mechanical means, with which all orthodentists are familiar, for bringing about changes and for stimulating growth at certain points in the jaw, have made it particularly desirable to know how and just where in the structure of the jaw these mechanical appliances bring about or stimulate the deposition of new bone. This study, continued over a number of years with the aid of animal experiments where both mechanical appliances and madder feeding could be made use of, has not only produced highly interesting and illuminating results; it has given a demonstration equally convincing for our immediate thesis. It has shown how indispensable is coöperation of more than one department of medicine in prosecuting such an inquiry. For example: Starting in the department of pharmacology, very early in the inquiry the investigator's work drew him into the department of physiology; at a stage not much later he found himself working also with the departments of anatomy and chemistry.

For Closer Coöperation. This is typical, and so far as I know universal, in all our research work. We can do effective research only by the fullest and freest coöperation of practically all the departments of medicine. These examples from the research laboratory will tend, I think, to corroborate and establish the reasoning drawn from the fields of dental education, from daily practice and from the clinics that holds that the line of progress for dentistry and medicine alike is that of interdependence and close coöperation. It might be said of the various divisions and specialties of medicine, as it was said by St. Paul of old, "No man liveth unto himself." Isolation is impossible, where it is not suicidal, and the progress of each is to the advantage of all.

Conclusion. Sound progress of the dental division of medicine is one which ought to be welcomed by every thoughtful physician, because it means lifting one more division of the whole practice of medicine onto a more intelligent, a more scientific and a more efficient basis. We are all, whether we will or no, part of the same body of learning and practice. None of us can be depressed or unworthy without affecting unfavorably the whole body. None of us can make advances in knowledge or skill or character without once more lifting the level of the whole, and so the medical profession at large will find it is to its interest and to its credit to foster every advance that is made by the dental branch of the healing art.

DETERMINATION OF THE PHAGOCYTIC POWER OF WHOLE BLOOD OR PLASMA-LEUKOCYTE MIXTURES FOR CLINICAL OR EXPERIMENTAL PURPOSES.*

DESCRIPTION OF AN IMPROVED METHOD, WITH REPRESENTATIVE FINDINGS.

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THE efficiency of the blood in clearing itself of bacterial invaders under given conditions is obviously a factor which enters intimately into many problems of infectious disease. Will a given infection spread or be self-limited; will therapeutic serum help, and, if so, what serum and in what dosage; has the patient's normal resistance become reinforced as a result of vaccination or infection? Any of these questions could obviously be considered more intelligently if the ability of the patient's blood stream to clear itself of the bacteria in question could be determined.

Under certain circumstances direct determination of the bactericidal power of whole blood is practicable. Indeed, studies by Robertson and others[1,2] of the pneumococcidal power of whole blood have greatly illumined many problems of pneumococcus infection in man and lower animals. However, attempts to measure the bactericidal power of the blood against, for instance, staphylococci and certain streptococci have been by no means so successful as against pneumococci.

Phagocytosis is the principal means by which bacteria are cleared from the blood stream. Direct bactericidal action by sensitizer and complement is known to occur with only a few bacteria; for the majority of pathogens, phagocytosis is the only known means of destruction. A simple quantitative method of estimating the phagocytic power of whole blood should, then, have many uses.†

* This investigation has been aided by a grant from the Faculty Research Committee of the University of Pennsylvania.

† In clearing bacteria from the circulating blood phagocytosis by macrophages in liver, spleen, lung and elsewhere is probably of equal or greater importance than phagocytosis by circulating polymorphonuclear leukocytes.[3,4] Macrophages and polymorphonuclears have been shown to respond similarly to phagocytosis-promoting substances, however, under a variety of circumstances.[5] The phagocytic power of the polymorphonuclear leukocytes in blood, we believe, therefore, can be used at least as an approximate indication of the total clearing power of the blood.

Among the earlier studies of phagocytosis which have become classics are the brilliant experiments of Wright and Douglas,[6] which first disclosed the normal phagocytosis-promoting substances named by these authors "opsonins." It is strange, however, that the essential technique used in these pioneer experiments should have persisted as the current clinical method of estimating phagocytic power for the succeeding 30 years.[7, 8, 9] To appreciate the confusion introduced through the imperfections of the Wright technique requires merely a study of the literature.[10] Zinsser and Bayne-Jones say of it:[9] "Measurements of opsonic indices are subject to so much experimental variation that they cannot be done with sufficient accuracy in clinical laboratories without an amount of labor that renders them useless as practical procedures."

The procedure described below was developed in the hope of providing a simple, accurate and practicable measure of phagocytic power. We are finding it useful.

Procedure. *Anticoagulant.* Prepare a stock solution of purified heparin (Hynson, Westcott and Dunning) by dissolving 25 mg. in 5 cc. of 0.85% sodium chlorid solution. This solution can be sterilized by autoclaving. The amount of the freshly prepared solution we have used with 1 cc. of human blood is 0.05 cc. of the stock solution; for dog blood, 0.1 cc. of the stock solution has been used. The presence of the anticoagulants which precipitate calcium is known to interfere with phagocytosis.[11, 10] We have not detected any interference with phagocytosis by purified heparin, or for that matter in using the less expensive unpurified product.

Preparation of Bacterial Suspension. A reproducible suspension of evenly suspended microörganisms is desired. In work with pneumococci we have used 19-hour cultures in infusion broth adjusted before autoclaving to pH = 8 with phosphate buffer. The bacteria were washed twice and resuspended in buffered broth. A bacterial count has then been made in a Petroff-Hausser counting chamber, and the density adjusted to about 6 billion organisms per cc. With bacteria that are more readily phagocytized than smooth pneumococci, less dense suspensions are used.

The Agitator. Some means of securing a uniform and reproducible amount of agitation of the phagocytic mixture is necessary for precise work. A suitable apparatus, which has been made available by the A. H. Thomas Company (Fig. 1), consists of a copper water bath containing a movable copper test-tube rack, a universal motor for 110 volts a.c. or d.c., and a gas microburner with attached stopcock mounted on a baseboard with switch and necessary wiring connections. The motor is geared to swing the movable test-tube rack to and fro approximately 280 times per minute. The rack takes 16 tubes, 15 by 85 mm. By means of the gas burner with stopcock for adjustment of the gas flow, a temperature of approximately 37° C. can be maintained in the water bath. Clips are provided within the bath for conveniently holding a suitable thermometer.

The Test. 1. Place 0.05 cc. of stock solution of purified heparin in a test tube for each cc. of blood to be obtained.

2. Obtain blood by venous puncture and place in tube containing the heparin. Mix gently.

3. Place 0.5 or 1 cc. of heparinized blood in a short test tube, 15 by 85 mm., and place in agitator bath. The water in the bath should be between 37° and 38° C.

4. Add 0.1 cc. of bacterial suspension to the blood; note time and mix quickly by gentle agitation. Start agitator.

5. At regular intervals remove by means of capillary pipette sufficient blood for making a smear in the same way as is usual for differential counts of blood. This can be done without stopping the agitator by dipping the pipette in the blood and removing quickly. A new pipette should be used for each interval. The slides should be perfectly clean and the ones used for spreading the film should have the corners cut off, so that the width of the film will be somewhat smaller than the width of the slide. This is done so that the edges of the film may be more easily examined. The interval of time that has proven satisfactory in most of our studies has been 3 minutes. In some instances where phagocytosis is rapid, 1-minute intervals were used. The smears should be thin enough to dry rapidly.

6. Fix the smears in methyl alcohol for 10 minutes.

FIG. 1.—Shaker for phagocytosis tests.

7. Use Giemsa stain, so adjusted with a weak solution of sodium carbonate that the bacteria and cells stain well. It is advisable to make a few extra slides at the end of the test for the purpose of testing the stain before staining the test slides. Other suitable blood stains may, of course, be used.

8. When making smears by the method just described, it will be found that the neutrophils are much more numerous along the edge of the film. This arrangement of the cells facilitates the examination by making it easy to locate the cells, and prevents the possibility of counting the same cell twice. The smear is examined by focusing the edge at one end and examining the cells found along or near the edge, always moving the slide in one direction. If sufficient cells are not found the other edge should be examined. The cells should be classified as positive or negative for phagocytosis. The results are expressed in terms of percentage of positive cells. At least 100 cells should be classified. Cells which are so clumped that their cyto-

plasm cannot be easily outlined or cells which are broken up or degenerated should be disregarded. Only cells which have organisms within their cytoplasm should be considered positive. When bacteria are merely adherent to the cell or appear partly ingested, the cell should be classed as negative.

9. Curves can be obtained by plotting the percentage of positive cells against the time intervals.

Test for Phagocytosis by Plasma-leukocyte and Serum-leukocyte Mixtures. Tests with plasma-leukocyte and serum-leukocyte mixtures are conducted as outlined above for whole blood. The only special feature requiring detailed discussion is the collection of the leukocytes.

A Method of Collecting Human Leukocytes. Collection of leukocytes by the "buffy-coat" method from small amounts of blood* did not satisfy our requirements as to yield of leukocytes and absence of erythrocytes. It seemed possible that, allowing the blood to sediment, the erythrocytes would settle first, leaving the leukocytes above, and that by removing the plasma at the proper time, it would contain the leukocytes with very few erythrocytes. This was first tried with citrated blood. The blood was removed by venous puncture and 0.5 cc. of 3% sodium citrate was added to each 5 cc. of blood. A total white cell count was made. Several sedimentation tubes were filled with blood and were allowed to settle. At half-hour intervals the plasma was removed and the number of leukocytes in the plasma removed was counted. To our surprise the number per c.mm. in the plasma at the end of the first period not only equaled the original count, but far exceeded it. This was an unexpected phenomenon. For fear of technical error, more tests were conducted with similar results. Some of these are shown in Table 1.

TABLE 1.—CONCENTRATION OF LEUKOCYTES IN PLASMA LAYER ABOVE SEDIMENTING ERYTHROCYTES.

Blood sample A: leukocyte count, 5200.			Blood sample B: leukocyte count, 5100		
Interval, hr.	Height of plasma taken, mm.	Leukocyte count.	Interval, hr.	Height of plasma taken, mm.	Leukocyte count.
½	8	12,000	½	4	16,450
1	10	14,400	1	5	12,350
1½	6	10,700	1½	6	11,500
2	5	9,000	2	4	9,000
2½	5	6,000	2½	3	5,000
3	5	3,400	3	2½	1,000

Mixed plasma A: Total plasma recovered, 2 cc.; leukocyte count on mixed plasma, 10,000; percentage of leukocytes present in whole blood recovered in plasma, 38%.

Mixed plasma B: Total plasma recovered, 3 cc.; leukocyte count on mixed plasma, 7000; percentage of leukocytes present in whole blood recovered in plasma, 41%.

To check these observations in another way, a sample of horse blood was obtained by venous puncture and placed in a small tube. There was marked sedimentation of the erythrocytes before coagulation took place. The clot was then fixed, sectioned and stained with hematoxylin and eosin. Examination of the sections showed a marked increase of leukocytes in the top portion of the clot as compared with the bottom portion; the top portion was, of course, relatively free from erythrocytes.

It seems that this phenomenon may be explained by the fact that the erythrocytes have a higher specific gravity and, therefore, settle more

* However, a satisfactory method of obtaining a "leukocytic cream" from larger volumes of blood has recently been described by Strumia.[12]

rapidly than the leukocytes, thus leaving the leukocytes in the upper strata of plasma. If the erythrocytes settle rapidly, the displacement of the plasma at the bottom by the cells will cause currents sufficient to carry some of the leukocytes upward and thus increase their number in the supernatant plasma. When the settling of cells is slowed or stopped, the leukocytes then settle to form a layer on top of the red cells (so-called "buffy coat").

Our earlier observations were made with blood from clinic patients who no doubt were not normal and had increased sedimentation rates of their erythrocytes. Subsequent studies with blood from normal individuals showed the same phenomenon, although less pronounced, and the amount of plasma-leukocyte mixture removed was too small to be of practical value. It then became necessary to accelerate the sedimentation of the erythrocytes and thereby allow the removal of more plasma-leukocyte mixture in order to increase the number of leukocytes recovered.

This was accomplished by removing a little over one-half of the erythrocytes by the following method: Place blood in test tube and centrifuge at moderate speed for 5 or 6 minutes; remove cells from the bottom by means of a capillary tube so bent that one end can be inserted in the tube to the bottom; the other end will reach a few inches below the bottom of the tube on the outside; by suction a syphon is established and the cells removed drop by drop until less than one-half remain. The tube is then removed and the remaining cells are resuspended by tipping back and forth gently. This blood will now settle rapidly; consequently more plasma and leukocytes can be recovered.

All the factors which influence the sedimentation rate[13] naturally influence this phenomenon and the collection of leukocytes by this method. Those accelerating sedimentation, such as body temperature and tilting of the sedimentation tube, can be used to advantage. Sedimentation should be started as soon as possible after withdrawal of the blood. Having the leukocytes in a high column of plasma facilitates their removal, as it does not necessitate the removal of plasma close to the erythrocyte zone. We have found it advisable to have the column of blood at least 100 mm. high; but this, of course, will vary according to the amount of blood available and the number of leukocytes desired.

The plasma so collected contains leukocytes and platelets with very few erythrocytes. By centrifugalizing slowly for a few minutes the majority of the leukocytes may be thrown down; the majority of the platelets may then be removed with the supernatant plasma. The leukocytes are carefully resuspended in the desired volume of suspending medium.

We have used as anticoagulants sodium citrate, sodium and potassium oxalate and heparin with good results. If the leukocytes are intended for phagocytosis, heparin should be used, or else the leukocytes should be carefully washed before using. Attempts to recover leukocytes from defibrinated blood by this method have not been particularly successful.

Method of Collecting Leukocytes. The following is an outline of a method for collecting human leukocytes based on the facts discussed:

1. Obtain blood by venous puncture. The amount will depend upon the number of cells desired.
2. Place in tube containing anticoagulant.
3. Centrifuge at moderate speed.
4. Remove a little over one-half of the erythrocytes from the bottom of the tube by means of capillary tube, or in any manner which will not disturb the "buffy coat." If the blood is from an anemic person or has an accelerated sedimentation rate this step can be omitted.
5. Gently mix the remaining cells with the plasma.
6. Place the blood in a tube of such diameter that the column will be at least 100 mm. high.

7. Place the tube in incubator and incline slightly.
8. Remove the plasma from top with capillary pipette at end of ½ and 1 hour. The time of collection may be varied according to the rate of sedimentation. If it is necessary to obtain as many leukocytes as possible, the collection should extend until no more plasma is available.
9. A total and differential white cell count may be made if it is necessary to determine the number and kind of leukocytes recovered.

The number of leukocytes recovered by this method depends: (1) Upon the number of leukocytes present in the original sample of blood; and (2) on the factors influencing the sedimentation rate of the erythrocytes. We have been successful in most cases in recovering from 20 to 60% of the leukocytes present in the original sample. In all cases we have been able to recover far more leukocytes which are relatively free from associated erythrocytes than we could expect to by the "buffy coat" method.

Representative Data on the Phagocytic Power of Whole Blood and of Plasma-leukocyte Mixtures. Data obtained by these methods (Fig. 2) are plotted as rate curves expressing the percentage of neutrophils which have phagocytized in the successive time intervals.

Relative Resistance to Phagocytosis of Different Bacterial Strains. Resistance to phagocytosis is known to be a major factor in determining virulence, for instance, of pneumococci. In the experiment recorded in Fig. 2, *A*, 1-cc. samples of heparinized human blood were mixed with 0.1 cc. of twice-washed pneumococcus suspension containing in each case approximately 600 million microörganisms. Four strains of pneumococci were used, *i. e.*, fully virulent Types I and II smooth strains (I S and II S), a laboratory strain of Type III smooth of moderate virulence (III S), and an avirulent rough strain originally derived from Type I (I R). It is evident that phagocytosis of Type I S was negligibly slight, of Type II S little more, of Type III S moderate and of the rough strain rapid and extensive.

Titration of Phagocytosis-promoting Action of Therapeutic Serum. In the experiment recorded in Fig. 2, *B*, the phagocytosis-promoting action of a therapeutic antipneumococcus horse serum* against the same virulent strain of Type I S was titrated. Serial dilutions of the horse serum were added to 1-cc. portions of human blood so as to give the final dilutions of horse serum shown in the figure; 600 million twice-washed pneumococci were added to each portion of blood. It is clear that the serum in dilutions of 1 to 200 and 1 to 400 had little or no effect on phagocytosis, that in a dilution of 1 to 100 a slight phagocytic response was obtained, and that in dilutions of 1 to 25 and 1 to 50 the phagocytosis-promoting action was very effective.

Inhibition of Phagocytosis. The carbohydrate capsular materials of pneumococci are known to have an extremely important effect in inhibiting phagocytosis.[14] This effect is a major factor in the

* For the horse serum we are indebted to the Mulford Laboratories of Sharp & Dohme.

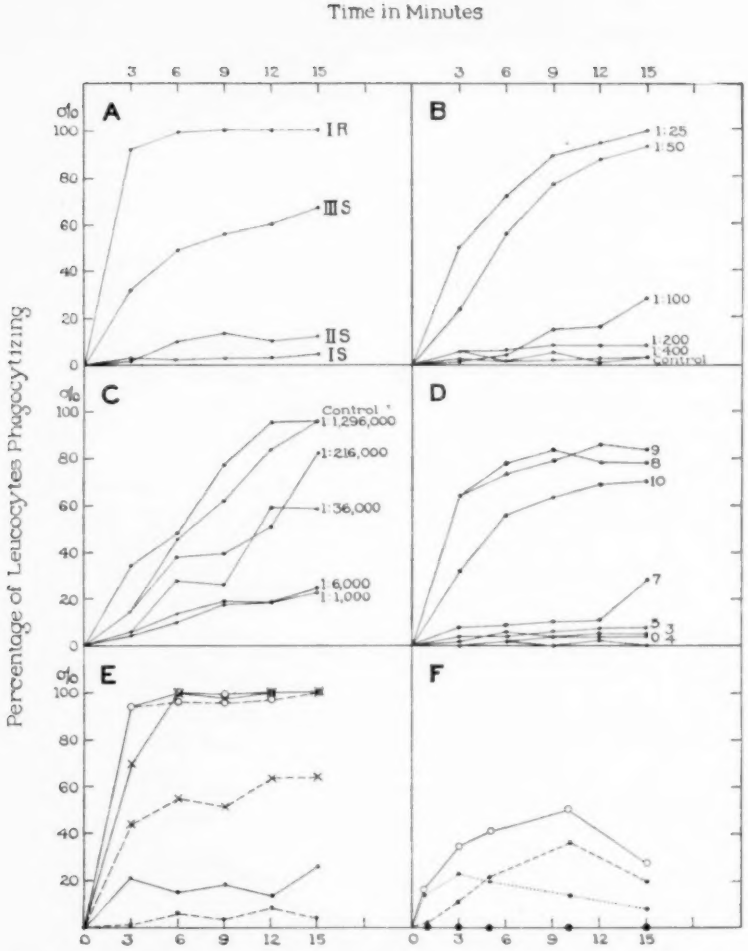

FIG. 2.—*A* through *E*, Rates of phagocytosis of bacteria by polymorphonuclear leukocytes in whole blood. *A*, Human blood. Pneumococci of Types I, II and III, smooth, and rough derived from Type I; 600 million twice-washed pneumococci in buffered broth added to each 1-cc. portion of heparinized blood. *B*, Human blood (1 cc.) plus 0.1 cc. of serial dilutions of therapeutic antipneumococcus horse serum; final dilutions of horse serum given in figure; 600 million twice-washed Type I S pneumococci in buffered broth added to each tube. *C*, Human blood containing antipneumococcus horse serum added to a suspension of Type I S pneumococcus containing serial dilutions of Type I S.S.S. Dilution of horse serum in the final mixture, 1 to 50. The initial dilutions of S.S.S. are indicated on the graph; to obtain dilutions in the final mixture multiply by 13. *D*, Dog blood. Numerals indicate days following infection with Type I pneumococcus—600 million twice-washed pneumococci in buffered broth added to 1 cc. of blood. *E*, Blood of patient with eosinophilia. Solid lines, neutrophils; broken lines, eosinophils. Open circles, Staphylococcus aureus, heavy suspension. Solid circles, pneumococcus Type I S; 600 million pneumococci added to each cc. of heparinized blood. Crosses, pneumococcus Type I S plus antipneumococcus horse serum; dilution of horse serum in the original mixture, 1 to 75. *F*, Human plasma–leukocyte mixture (Type O), plus erythrocytes (Type A); 50 million erythrocytes added to 0.5 cc. of plasma containing 18 million leukocytes. Dotted line, leukocytes containing stainable erythrocytes. Broken line, leukocytes containing vacuoles. Solid line, sum of leukocytes containing stainable erythrocytes and vacuoles. Solid circles along baseline, same plasma-leukocyte mixture plus Type O erythrocytes; no phagocytosis.

so-called "aggressive action" of pneumococci and other bacteria.[15] In the experiment shown in Fig. 2, *C*, such an inhibitory action is shown. The therapeutic horse serum was added to portions of the same human blood used in Fig. 2, *B*, so as to give a dilution of 1 to 50 horse serum in the final mixture. Dilutions of deacetylated Type I carbohydrate specific soluble substance* were added to the twice-washed pneumococcus Type I suspension. The blood samples containing horse serum and the pneumococci containing carbohydrate solution were then mixed and phagocytosis tests were run. Marked inhibition of the phagocytosis-promoting action of the therapeutic serum was obtained with all dilutions of soluble substance of 1 to 216,000 or less.

Development of Antibodies Following Infection or Inoculation. In the course of studies on the effect of pneumothorax on experimental pneumonia in dogs,[16] virulent Type I pneumococci have been injected in dogs intrabronchially by Dr. Louis Lieberman. The development of phagocytosis-promoting antibodies in a dog so infected is shown in Fig. 2, *D*. One-cc. portions of the dogs' blood were mixed with 600 million twice-washed Type I pneumococci and phagocytosis tests were run. The numerals in Fig. 2, *D*, indicate the days after infection on which the blood samples were taken for test; sample O was taken just before infection. It is evident that no detectable antibody response occurred for 5 days after infection. No test was made on the sixth day. The seventh day, phagocytosis-promoting antibody was detected and was prominent on the succeeding days.

The dog sera studied for phagocytosis-promoting power were tested also for agglutination and mouse protection. The results of the three tests were in general parallel. The phagocytosis test proved, however, to be distinctly more delicate than agglutination, and in a majority of instances also more delicate than mouse protection; in several cases the appearance of antibodies was detected a day or more earlier by phagocytosis than by the other tests.

Phagocytosis by Cells Other Than Normal Neutrophils. The technique of studying phagocytosis in whole blood affords an opportunity to compare under identical conditions phagocytosis by normal neutrophils with phagocytosis by any other cells which may appear in the blood in sufficient numbers. For instance, in looking over many slides the impression has been gained from the occasional eosinophil encountered that these cells were phagocytic but less actively so than the neutrophils.

An opportunity to check this observation was afforded by a patient with eosinophilia of unknown origin. The total count was 12,200 leukocytes per c.mm., of which 5612 were neutrophils (46%), 4148 lymphocytes (34%), 488 monocytes (4%) and 1952 eosinophils (16%). One-cc. portions of this patient's blood were added

* For this we are indebted to Dr. Walther Goebel, of the Rockefeller Institute.

to 600 million smooth Type I pneumococci and to a heavy suspension of Staphylococcus aureus; also a portion of the blood containing 1 to 75 antipneumococcus horse serum was added to 600 million Type I S pneumococci. Phagocytosis tests were run and the rate curves for phagocytosis by neutrophils and eosinophils were separately determined (Fig. 2, *E*). It is evident that phagocytosis of pneumococci by neutrophils definitely exceeded that by eosinophils both with and without serum. With the staphylococcus this superiority of the neutrophils was not so apparent from the graph. Another method of analysis shown in Table 2 does bring out this superiority of neutrophils, however, with respect to ingestion of staphylococci as well as of pneumococci.

TABLE 2.—PHAGOCYTOSIS BY EOSINOPHILS AS COMPARED WITH NEUTROPHILS.

1 Cc. of Blood Plus Pneumococcus Type I S.

Number of bacteria per cell.	Time in minutes.				
	3.	6.	9.	12.	15.
Eosinophils (100 observed):					
Over 10	0	0	0	0	0
5 to 10	0	0	0	0	0
1 to 5	1	6	3	8	4
Neutrophils (100 observed):					
Over 10	1	1	0	1	0
5 to 10	2	1	0	0	1
1 to 5	18	13	18	12	26
1 Cc. of Blood Plus Antipneumococcus Serum (1 to 75) Plus Pneumococcus Type I S.					
Eosinophils (100 observed):					
Over 10	6	8	11	17	10
5 to 10	10	12	11	16	18
1 to 5	28	35	29	31	36
Neutrophils (100 observed):					
Over 10	30	65	90	93	88
5 to 10	20	19	5	5	4
1 to 5	20	15	3	2	8
1 Cc. of Blood Plus Staphylococcus Aureus.					
Eosinophils (100 observed):					
Over 10	23	68	68	72	80
5 to 10	36	16	15	13	10
1 to 5	35	12	13	12	10
Neutrophils (100 observed):					
Over 10	86	100	99	100	100
5 to 10	28	0	0	0	0
1 to 5	6	0	1	0	0

Type Specific Phagocytosis-promoting Antibodies in Human Blood. The opsonization of human erythrocytes by human sera of incompatible types was demonstrated, in 1925, by Schiff.[17] This "isohemotropin" effect was found in only a certain proportion of human bloods; it occurred in association with isohemolysis and with isohemagglutination of relatively high titer.

We have confirmed these findings of Schiff, using first whole blood and later plasma-leukocyte mixtures prepared as outlined above. A representative result is given in Table 3. Fifty million erythro-

cytes of each type were added to plasma-leukocyte mixtures as indicated. The results of isohemolysis tests and the isoagglutination titers are given in the last columns of the table. The percentage phagocytosis at the several time intervals includes leukocytes containing stainable erythrocytes (*E*) and those containing only vacuoles of the size and shape of erythrocytes (*V*).

These vacuoles were interpreted as stromata of hemolyzed erythrocytes. This interpretation was confirmed by direct observation of the process of phagocytosis in film preparations[18] in a warm box, using a Zeiss cardioid dark-field condensor. Erythrocytes and hemolyzed stromata ("ghosts") can thus readily be distinguished. Using Type A erythrocytes sensitized with a Type O plasma which contained isohemolysin, the ingestion both of unlyzed erythrocytes and of ghosts was observed. Many of the ingested erythrocytes were hemolyzed intracellularly, and digestion and disappearance of the red cells and stromata regularly followed ingestion.

It will be observed that in Table 3, and this is representative of other similar data we have obtained, Type O plasma caused phagocytosis of Types A, B and AB cells, Type A plasma of B and AB but not of O cells, and that Type AB plasma caused no phagocytosis. This is in accord with expectation from the known distribution of isoantigens and antibodies. Type B plasma did not cause phagocytosis or hemolysis and was exceedingly weak in isoagglutination. This failure to promote phagocytosis or hemolysis we have found in the several B plasmas tested, but we have not yet analyzed the matter further.

Fig. 2, *F*, shows graphically the result of an experiment with O plasma and A erythrocytes. This plasma was hemolytic. The dotted line indicates the percentage of leukocytes containing stainable red cells and the broken line the percentage containing vacuoles. The solid line is the total percentage phagocytosis, *i. e.*, the sum of the percentages of stainable cells and vacuoles. The percentage of leukocytes containing unhemolyzed erythrocytes reached a maximum in 3 minutes, the percentage containing vacuoles, as would be expected, attained its maximum later, *i. e.*, at 10 minutes. After 10 minutes the rate of digestion and disappearance evidently surpassed the rate of ingestion of new elements, and the percentage phagocytosis thus appeared to fall. A similar effect due to intracellular digestion of typhoid bacilli has previously been described.[19]

Reliability of the Method. Current methods of estimating opsonic and phagocytic indices lose greatly in value through such sources of error as imperfect mixing, the use of anticoagulants which combine with calcium, and dependence on a single serum concentration and a single time of contact between phagocytes and test objects. We have sought to develop a method of direct estimate of phagocytic power, free from these errors, and suitable both for experimental and clinical use.

TABLE 3.—PHAGOCYTOSIS BY PLASMA-LEUKOCYTE MIXTURES OF ERYTHROCYTES OF INCOMPATIBLE TYPE.

Plasma, 0.5 cc.	Red cells, 50 million.	Leukocytes in millions.	1 min.		3 min.		5 min.		10 min.		15 min.		Plasma-leukocyte hemolysis.	Serum* hemolysis.	Agglutination† complete.
			E.	*V.*	*E.*	*V.*	*E.*	*V.*	*E.*	*V.*	*E.*	*V.*			
O	A	12.5	44	12	80	10	86	10	70	14	88	6	Positive	Positive	1–32
O	B	12.5	40	5	71	12	80	8	70	19	73	22	Positive	Positive	1–64
O	AB	12.5	30	8	91	7	90	8	93	7	91	7	Positive	Positive	1–64
A	O	10.2	0	0	0	0	0	0	0	0	0	0	Negative	Negative	Negative.
A	B	10.2	45	9	48	15	25	31	31	34	30	35	Positive	Positive	1–64
A	AB	10.2	20	12	34	13	34	13	29	26	29	21	Positive	Positive	1–32
B	O	28.0	0	0	0	0	0	0	0	0	0	0	Negative	Negative	Negative.
B	A	28.0	0	0	0	0	0	0	0	0	0	0	Negative	Negative	1–4
B	AB	28.0	0	0	0	0	0	0	0	0	0	0	Negative	Negative	Negative.
AB	A	9.0	0	0	0	1	0	0	0	0	0	0	Negative	Negative	Negative.
AB	B	9.0	0	0	0	0	0	0	0	0	0	0	Negative	Negative	Negative.
AB	O	9.0	0	0	0	0	0	0	0	0	0	0	Negative	Negative	Negative.

* Serum hemolysis slower and not as complete as the plasma-leukocyte hemolysis.

† Lowest dilution, 1 to 2.

TABLE 4.—DESCRIPTIVE STATISTICS FOR PHAGOCYTOSIS OF TYPE I PNEUMOCOCCUS BY NORMAL DOG BLOOD, BLOOD OF ACTIVELY IMMUNE DOGS AND NORMAL DOG BLOOD PLUS IMMUNE HORSE SERUM.

	Group.	Minutes of contact between blood and bacteria.																	
		3.				6.				9.				12.				15.			
		N.	*M.*	σ	*C.V.*	*N.*	*M.*	σ	*C.V.*	*N.*	*M.*	σ	*C.V.*	*N.*	*M.*	σ	*C.V.*	*N.*	*M.*	σ	*C.V.*
Normal dog blood	I	51	2.45	2.99	122	52	3.71	3.80	102	51	4.84	4.56	94	52	5.94	5.45	91	55	6.08	7.00	115
Immune dog blood	II	23	35.35	20.52	58	23	49.04	27.45	56	23	62.39	27.43	44	23	66.48	27.46	41	25	61.92	27.93	45
Normal dog blood + immune horse serum	III	15	35.40	29.48	83	15	68.47	25.38	37	15	81.20	16.93	20	15	86.67	15.32	17	14	87.79	12.43	14

N = Number of observations.
σ = Standard deviation of observations from the mean.
M = Arithmetic mean of per cent of cells showing phagocytosis in each observation.
C.V. = Coefficient of variation.

There remains for consideration the question as to what degree of precision and reliability may be expected of the method described. A general answer is not possible, since the reproducibility of the results depends upon factors peculiar to each system under consideration. However, in following the phagocytosis of virulent Type I pneumococci by the blood of dogs with experimental pneumonia, as described above, sufficient data have been obtained to permit of analysis by ordinary statistical methods (Tables 4 and 5).*

TABLE 5.—COMPARISON OF PHAGOCYTOSIS BY DOG BLOOD IN GROUPS GIVEN IN TABLE 1, AND PROBABILITIES, *P*, OF DIFFERENCES BEING DUE TO ERRORS OF RANDOM SAMPLING.

	Groups	Minutes of contact between blood and bacteria.									
		3.		6.		9.		12.		15.	
		d.	*P.*	*d.*	*P.*	*d.*	*P.*	*d.*	*P.*	*d.*	*P.*
Immune dog blood compared with normal dog blood	II–I	7.65	0	7.89	0	10.00	0	10.48	0	9.86	0
Normal dog blood plus immune horse serum, compared with normal dog blood	III–I	4.32	< .001	9.85	0	17.28	0	20.04	0	23.67	0

$$\text{Relative deviate} = d = \frac{M_2 - M_1}{\sqrt{\frac{\sigma_2^2}{N_2} + \frac{\sigma_1^2}{N_1}}}$$

The phagocytosis determinations are considered in three groups: Group I includes all determinations up to and including 96 hours after intrabronchial infection. Since no antibody response was detected up to this time, all these determinations are classed as upon "normal" dog blood. Group II includes all determinations upon dogs during the period when humoral immunity was well established, that is, from the eighth to the fourteenth day of infection, inclusive. Group III includes determinations upon dog blood, not of itself possessing immune antibodies, but with antipneumococcus horse serum added in a final dilution of 1 to 50. The percentages of neutrophils containing ingested bacteria are given separately in Table 4 for each time interval. N is the number of determinations in each category, M the arithmetic mean and σ the standard deviation of these determinations. *C.V.* is the coefficient of variation, a measure of relative dispersal, given by the formula,[20]

$$C.V. = 100 \frac{\sigma}{M} \%.$$

As compared with measurements of the sort more commonly given statistical treatment, the scatter of our values, as reflected in the standard deviations, is found to be great. It may be said, however,

* We are indebted to Dr. Louis Lieberman for permission to publish data on these dogs at this time.

that the system under consideration is a particularly sensitive one, subject to great influence in one direction by traces of phagocytosis-promoting substances in the serum, and in the other direction by the inhibiting action of traces of bacterial specific soluble substances (Fig. 2, *B*, *C*, *D*). The conditions, moreover, were only average laboratory working conditions; at least 4 different observers, for instance, were engaged in counting the phagocytes, and individual differences in interpretation are unfortunately by no means impossible.

The coefficient of variation is seen to decrease in each group as the time of contact between blood and bacteria increases from 3 and 6 minutes to 12 and 15 minutes. This substantiates the impression of the workers that errors in time of sampling were relatively great at the shorter time intervals. With a test object which was not altered within the phagocyte, greater reliability was, therefore, obtained at the longer intervals. When intracellular digestion occurs, however, as with erythrocytes (Fig. 2, *F*), typhoid bacilli[5] and certain other cells, observations at a longer time interval alone may be very misleading.

In Table 5 the significance of the differences between the several groups are examined for statistical significance. The relative deviate, *d*, is determined from the formula,

$$d_{1,2} = \frac{M_2 - M_1}{\sqrt{\frac{\sigma_2^2}{N_2} + \frac{\sigma_1^2}{N_1}}}.$$

The probability, *P*, that any given deviate may be due to errors of random sampling rather than to real differences inherent in the groups may be obtained from a suitable table of probability integrals.[21, 22] In the present data, values of *P* are infinitesimally small in all cases, even in that of the deviate between Groups III and I at the 3-minute interval, in which case there are about 8 chances in a million that the difference observed might be due to sampling error.

The method of determining phagocytosis described, therefore, shows differences between these samples of normal dog blood, blood of actively immune dogs and normal dog blood plus immune horse serum which more than adequately satisfy the criteria for statistical significance.

Summary. A method for direct determination of the phagocytic power of whole blood or plasma-leukocyte mixtures, human or animal, is described. The following features are designed to eliminate sources of error in current methods: (*a*) Replacement by heparin of anticoagulants which combine with calcium. (*b*) A technique for collecting leukocytes from small samples of blood with a minimum of mechanical or chemical manipulation. (*c*) Provision of an agitator to provide continuous mixing of phagocytes and test

objects. (*d*) Determination of percentage phagocytosis as a function of time.

Examples are given of the application of this method to a variety of problems, *e. g.*, titration of the phagocytosis-promoting action of therapeutic serum, detection of antibodies following infection or vaccination, the relative resistance to phagocytosis of different bacterial strains and inhibition of phagocytosis by soluble bacterial products.

The blood of a patient with eosinophilia examined by this method showed phagocytosis by eosinophils, which was, however, quantitatively inferior to that by neutrophils in the same blood.

The opsonization of human erythrocytes by human sera of incompatible types, described by Schiff, has been confirmed. Intracellular lysis and digestion of ingested erythrocytes has been observed.

The reliability and significance of results obtained with the blood of dogs during the course of experimental pneumococcus infections are examined statistically.

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EFFECT OF TISSUE EXTRACTS ON MUSCLE PAINS OF ISCHEMIC ORIGIN (INTERMITTENT CLAUDICATION).*

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Interest in the therapeutic use of various tissue extracts for circulatory diseases originated from the work of Frey and Kraut, in 1926, who isolated a substance from urine which lowered blood pressure when injected intravenously into animals. This substance was subsequently named kallikrein (later padutin) and was found by Frey[4] to inhibit the pain of angina pectoris and intermittent claudication, and to lower blood pressure in cases of hypertension when administered intramuscularly to human beings. Later Frey[5] found that the fluid from a pancreatic cyst had similar properties, and concluded that the effects of kallikrein were attributable to a hormone present in many tissues but elaborated in the pancreas. Gley and Kisthinios, and later Wolffe, Findlay and Dessen, described extracts of pancreatic tissue which gave therapeutically similar results. J. S. Schwarzmann prepared an extract of skeletal muscle, which he called myoston, and reported improvement in cases of angina pectoris after injecting it intramuscularly. M. S. Schwarzmann noted marked improvement in 3 cases of intermittent claudication after treatment with myoston. In small series of cases in which there was occlusive disease of the arteries of the leg and intermittent claudication, pancreatic tissue extract has been reported to have increased the walking distance, but controlled tests before medication was used were not mentioned. This effect on tolerance to exercise has been considered to be the result of vasodilatation. Experimental work in animals has shown that pancreatic extract and kallikrein produce a transient fall in blood pressure when injected intravenously, and cause dilatation of the coronary arteries when perfused into a rabbit's heart;[3] however, when perfused

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through the arteries of the leg of a rabbit, Nuzum and Elliot noted vasoconstriction. Topical applications of pancreatic tissue extract cause vasodilatation in the frog's foot and inhibit the effect of epinephrin on dogs when injected intravenously.[11] The physiologic properties have been felt to be distinct from histamin and cholin[11] and from adenosin.[3]

It is noteworthy, however, that both the pancreatic tissue extract and myoston are undoubtedly mixtures of various organic compounds, and that when used therapeutically they have been injected intramuscularly, and not intravenously or by perfusion. Nuzum and Elliot were unable to demonstrate vasodilatation in animals after intramuscular or subcutaneous injections of kallikrein. Actual evidence is lacking that the therapeutic effects observed in cases of intermittent claudication are due to vasodilatation.

Intermittent claudication is one of the most constant and significant symptoms seen in medical practice. It results from the occlusion of the larger arteries of the extremities, due either to thromboangiitis obliterans or to arteriosclerosis obliterans in 90% of our cases. Patients describe intermittent claudication as a pain, ache, cramp or sense of extreme fatigue localized in certain muscle groups and induced by a certain amount of muscular exercise. If the exercise is continued, muscular spasticity and weakness, and sometimes true cramp, are added to the pain. This pain or sense of fatigue is never present during rest, and it is relieved in a few minutes by cessation of the muscular effort without change in posture. The amount of muscular effort necessary to produce intermittent claudication is remarkably constant during any one phase of the individual's disease.

We have studied the effects of pancreatic tissue extract, of two types of skeletal muscle extract and of adenosin, on intermittent claudication. The cutaneous temperature of the digits was measured in a room of controlled temperature, to determine whether significant vasodilatation occurred.

In order to evaluate the effect of the various tissue extracts, it was necessary to have a standardized test for claudication. Our test is as follows: After a rest of one-half hour, the patient walks on a level floor, with one of us as a pacemaker, at the rate of 120 steps per minute, until sufficient distress occurs to cause him to stop. The time elapsed from the beginning of the walk until cessation of it is designated as the "claudication time." Although this involves a factor of subjective sensation in determining the end point, objective evidence, such as limping, muscular weakness or spasticity usually precedes this end point. Sixteen patients with occlusive arterial disease were tested repeatedly on various days in the same environmental temperature and have shown an average variation of only 10% from their shortest claudication time. The maximal variation was 20%. The claudication time

was determined and frequently was verified 2 or 3 times before the extracts were given. The extract was then injected into the triceps muscle of the arm; hot, moist towels were applied and the muscle was gently massaged.

Pancreatic Tissue Extract. The first extract studied was the insulin-free pancreatic tissue extracts,* which Wolffe previously had described and standardized by means of its power to neutralize epinephrin. The dose was arbitrarily fixed at 3 cc., as this seemed to give the maximal effect in the majority of cases; however, in a few instances a greater effect was noted after injection of 4 or 5 cc. Some variation was noted in the potency of the various lots of this extract.

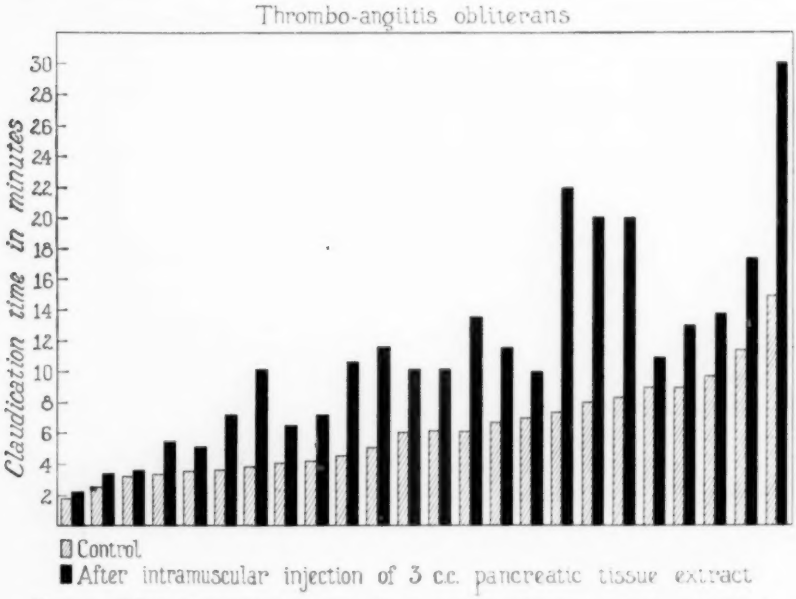

FIG. 1.—Effect of pancreatic tissue extract on intermittent claudication in twenty-four cases of thromboangiitis obliterans.

We have previously reported[2,8] the effect of this extract on 22 patients with definite occlusive arterial disease of the legs. Since that time we have tested 33 additional patients (Figs. 1 and 2). In the entire series of 55 cases, the diagnosis of arteriosclerosis obliterans had been established definitely in 20 cases, and thromboangiitis obliterans in 35 cases; all of the patients had typical intermittent claudication. The results for the entire series have been similar to those noted in the original 22 cases. Definite lengthening of claudication time was noted in 50 (92%) cases, and the average

* Tissue extract No. 568, Sharp & Dohme.

claudication time for the entire group was increased 1.85 times. The average results were slightly better in the group of cases of thromboangiitis obliterans than in the group of cases of arteriosclerosis; in the former, the increase, as compared with the control test, was 1.98 times, and in the latter, 1.65 times. In 6 cases no claudication was produced after 20 minutes of standard walking. The poorest results were noted in cases in which the control claudication time was short and in which marked degrees of arterial insufficiency of the legs were present. Generally, definite improvement was noted $1\frac{1}{2}$ to 2 hours after the injection, but the maximal improvement usually occurred after 24 hours. The increased claudication time was maintained for from 2 to 7 days, usually 4 days, after which there was gradual return to the original claudication time.

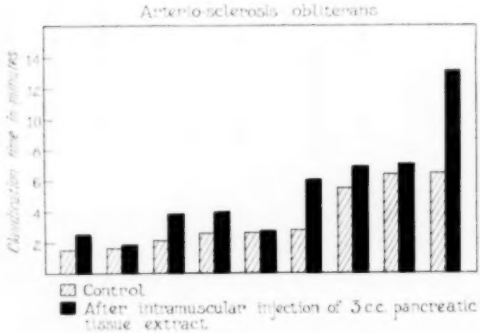

FIG. 2.—Effect of pancreatic tissue extract on intermittent claudication in 9 cases of arteriosclerosis obliterans.

Extract of Skeletal Muscle (Myoston).* The skeletal muscle extract was prepared according to the method of J. S. Schwarzmann, and it was standardized on the basis of its content of adenosin phosphoric acid, 1 cc. containing 2.5 mg. Myoston was given intramuscularly, by the same technique as that employed in giving the pancreatic extract, to 13 patients, 5 of whom had arteriosclerosis obliterans and 8 thromboangiitis obliterans. All of them had constant, intermittent claudication. The results which are given in Fig. 3 were similar in effect and in duration of effect to those following use of the pancreatic extract in the cases of thromboangiitis obliterans. In all, there was definite lengthening of the claudication time; the average was 2.1 times the control average. However, in only 1 of the 5 cases of arteriosclerosis was any marked improvement noted.

Myoston was administered orally in amounts of from 5.3 to 16 cc., over periods of from 1 to 3 days, to 8 patients; 2 with arteriosclerosis

* Myoston: Dr. George Henning (Chem. u. pharm. Fabrik), Berlin.

obliterans and 6 with thromboangiitis obliterans. Definite increase of claudication time occurred in 75 per cent of the cases, and the average claudication time was 1.8 times that of the control test (Fig. 4). This effect did not last more than 2 days.

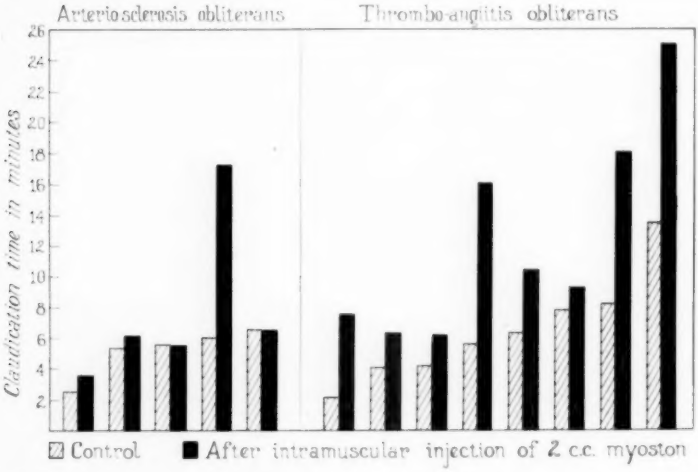

FIG. 3.—Effect of skeletal muscle extract (myoston), injected intramuscularly, on intermittent claudication in arteriosclerosis obliterans and thromboangiitis obliterans.

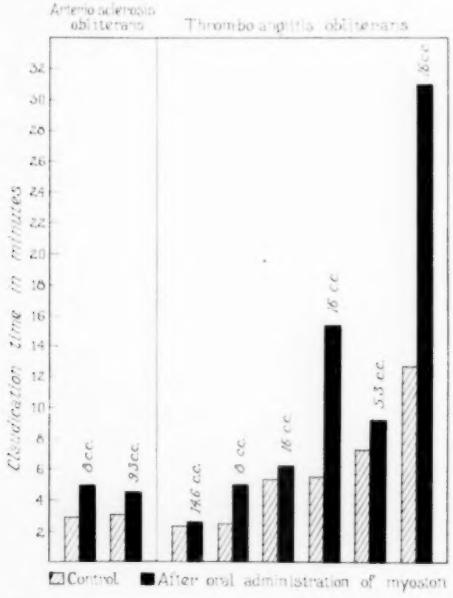

FIG. 4.—Effect of skeletal muscle extract (myoston), administered orally, on intermittent claudication in arteriosclerosis obliterans and thromboangiitis obliterans.

Muscle Adenosin Phosphoric Acid. More recently we have studied the effects of another muscle extract, muscle adenosin phosphoric acid (M.A.P.), obtained from the same source as myoston. This extract was administered intramuscularly in doses of 20 mg. in a 1% solution to 4 patients, 2 with arteriosclerosis obliterans and 2 with thromboangiitis obliterans; all of the patients had intermittent claudication. The effects are shown in Fig. 5. Definite lengthening of claudication time was noted in all the cases, but the average was only 1.6 times the control claudication time.

Adenosin. It has been suggested that adenosin or adenosin phosphoric acid was the active portion of all of these extracts.

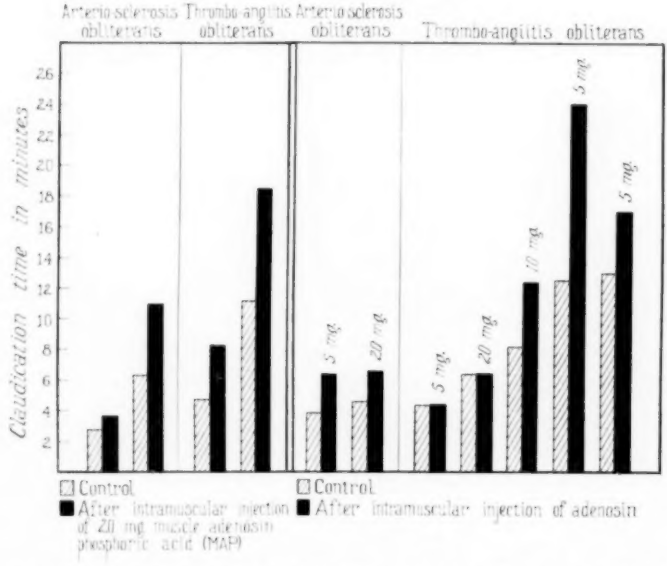

FIG. 5.—Effect of muscle adenosin phosphoric acid and adenosin on intermittent claudication in arteriosclerosis obliterans and thromboangiitis obliterans.

We tested the effect of pure adenosin given intramuscularly in physiologic solution of sodium chlorid, in amounts of from 5 to 20 mg. It was given to 7 patients, 2 with arteriosclerosis obliterans and 5 with thromboangiitis obliterans (Fig. 5). In 2 cases of the latter group lengthening of the claudication time did not appear. The average increase was 1.4 times that of the control claudication time. Thus, the average results with adenosin and muscle adenosin phosphoric acid were slightly inferior to those with pancreatic tissue extract, which has a very small content of adenosin phosphoric acid.

None of the patients tested with any of the extracts had untoward effects. There was usually moderate pain of short duration at the

site of the injection, but there were no chills, fever or evidences of histamin-like or foreign protein reactions.

Effects on Surface Temperature. The effect of pancreatic tissue extract on the cutaneous temperature of the toes, as a measure of vasodilatation, has been negligible in our experience. In 3 cases, temperatures of the skin were observed for 24 hours, immediately before and immediately after administration of 3 cc. of the extract. The curves were practically identical. In 12 other cases, in which the cutaneous temperatures were observed, during a control period, and for at least 2 hours after administration of the extract, the maximal rise was 2.9° C., and this lasted only 1 hour; the average rise was 0.8° C. In 3 cases, in which similar tests were made after intramuscular administration of myoston, the maximal rise was 1.6° C. and the average 0.3° C. In 2 of 3 cases, following administration of muscle adenosin phosphoric acid, there was definite vasodilatation, shown by a transient rise of 3.2° C. This may have been due to the greater content of adenosin, for in 3 cases in which pure adenosin was given the rise in temperature was 4.6° to 8.2° C. This vasodilatation lasted only 1 to 2 hours, and on the following day, when the cutaneous temperatures had returned to their basic levels, the claudication time was most greatly increased. In 4 cases in which repeated tests were made, both as to claudication time and cutaneous temperatures, each of the patients received several, or all, of the different extracts, with definite increase in claudication time. There was absolutely no correlation between claudication time and the cutaneous temperatures.

It has been our experience that definite vasodilatation does not significantly affect intermittent claudication. In 2 cases in which tests were made before and during artificially induced fever there was no increase in claudication time. In both of these cases there was definite increase with the extracts. Even after extensive intravenous treatment with typhoid vaccine, little effect has been noted on intermittent claudication.[1] In 1 case increase in claudication time was not noted either after 20 gr. (1.3 gm.) of theobromin, given orally, or later, after 0.2 gm. of theophyllin ethylenediamin, given intravenously, both of which produced definite vasodilatation. However, a 200% increase in claudication time was then noted after 16 cc. of myoston had been given by mouth over a period of 2 days. In 1 case, no difference in claudication time was noted during tests before, and 4 weeks after, lumbar sympathetic ganglionectomy, which caused a sharp increase in surface temperature, but there was a 100% increase after 3 cc. of pancreatic tissue extract had been given intramuscularly.

Comment. We feel that results of this study have confirmed, by actual measurement of work done, the opinions of certain previous investigators that pancreatic tissue extract and myoston, given intramuscularly, do inhibit or delay intermittent claudication in

the great majority of cases in which it occurs. The exact component of the extracts responsible for the effect is not known, but must be common to both the pancreas and skeletal muscle. In the present state of knowledge, the method of action also seems obscure. It has been our experience that the extracts have little or no effect on the pretrophic pain, or on the pain which results from the ulceration and gangrene which occurs in occlusive arterial disease. This seems to exclude analgesia. We cannot concur with the beliefs of previous investigators that in intermittent claudication the therapeutic effect of these tissue extracts, when given intramuscularly, is the result of vasodilatation. We have not demonstrated that definite index of the vasodilatation, namely, significant rise in cutaneous temperature, and the effects on claudication far exceed those observed after definite vasodilatation produced by drugs, sympathectomy or artificially induced fever. It seems probable to us that the therapeutic effect consists in supplying some substance to the actively contracting muscle which it cannot obtain in sufficient concentration, with a restricted supply of arterial blood. The evidence is not conclusive that adenosin phosphoric acid is the active substance, but it may have a similar action. Further studies are being carried out on this phase of the problem.

From the practical standpoint, the therapeutic value of the tissue extracts in peripheral arterial disease seems to us to be restricted to those cases in which intermittent claudication is the chief symptom and trophic lesions are not present. Individual testing is advisable in all cases, to note the extract and dosage that will give the optimal effect. Most patients seem to do satisfactorily on one injection a week. We have noted, in a number of cases, that after a series of 8 to 16 weekly injections of one of the extracts the improvement was maintained for several months. If myoston is administered by mouth it is necessary to give it at least on alternate days in fairly large doses, and the cost of a sufficient amount to maintain the effect over periods of time is almost prohibitive at present.

Summary. Definite lengthening of the time necessary to produce intermittent claudication during a standard claudication test was noted in 92% of a series of 55 cases of thromboangiitis obliterans and arteriosclerosis obliterans, following intramuscular injections of pancreatic tissue extract. Similar effects were noted in all of a series of 8 cases of thromboangiitis obliterans after intramuscular administration of myoston, a skeletal muscle extract. In only 1 of 5 patients with arteriosclerosis obliterans was an increase in claudication time noted after myoston had been given intramuscularly. In 75 per cent of a series of 8 cases of intermittent claudication, in which the patients received myoston orally, an approximately equal, but more transient, effect was noted. Definite, but less striking increases in claudication time were noted in 4 cases in

which patients received muscle adenosin phosphoric acid (M.A.P.) intramuscularly and in 4 cases in which patients received adenosin intramuscularly.

Evidence is presented to show that these effects are not the result of vasodilatation but are the result of some direct action on the contracting ischemic muscles.

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A STUDY OF THE SPUTUM IN PULMONARY ASBESTOSIS.

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So much has been written on pulmonary asbestosis during the few years which have elapsed since its first recognition (Cooke, 1924, 1927; Stuart McDonald, 1927; Merewether, 1930; Lynch and Smith, 1930; Kruger *et al.*, 1931; Ellman, 1933) that only a brief introductory statement is necessary here. The disease is a slowly progressive fibrosis of the lungs due to the inhalation of asbestos dust. The fibrosis is widespread, mainly basal and subpleural in distribution, and leads ultimately to such extensive destruction of the parenchyma that the most serious functional disability results. Death is usually brought about by some intercurrent infection, tuberculosis, influenza, or some form of pneumonia. The length of exposure to dust has varied within wide limits, but it is clear that gross disease may follow even as short an exposure as 18 months, provided the dust concentration has been sufficiently high. A certain interval of time must elapse before the disease seriously manifests itself, possibly a period of 7 years (Merewether, 1933–1934). At a certain stage of its development the disease can be diagnosed with great assurance on clinical and radiological

examination, the more so as a clear industrial history of exposure to asbestos dust is almost invariably available. In the earlier stages of disordered function it may be possible only to suspect that a lesion is developing.

The Asbestos Body. This has attracted much attention since it was first adequately described and its probable significance pointed out by Stuart McDonald (1927). A detailed description is given by Gloyne (1932). The bodies are formed in the lung aveoli by the deposition around individual asbestos fibers of an iron-containing silica gel, derived partly from the fiber, partly from the surrounding fluids. They are highly characteristic in form, while presenting considerable individual variation. The two chief varieties are: (1) a spindle-shaped elongated form, very slender in the center and swelling gradually to bulbous extremities, and (2) a beaded form, with the smallest elements in the center and a gradual increase in size to large terminal knobs. In the latter form, the central core of asbestos fiber can often be made out very clearly, especially if the body has been fractured, as often happens. The bodies, which range in size from a few up to several hundred microns, vary in color from pale green through golden yellow to deep brown, depending mainly on their size. They give the Prussian blue reaction with corresponding grades of intensity.

The bodies were first observed in sections of the lung, where they occur singly, in small groups and in radiating clumps in the alveoli, or embedded in the fibrous tissue of the grossly diseased areas. They were next recovered from lung juice obtained by exploratory puncture of the chest during life (Stewart and Haddow, 1929) and finally these observers were able to demonstrate their presence in the sputum of asbestos workers. Later Stewart, Tattersall and Haddow (1932) recovered clumps of bodies similar to those seen in the lung alveoli postmortem from 2 cases of asbestosis, one advanced and since dead of the disease, the other moderately advanced. They suggested that the presence of such clumps meant disintegration of lung tissue and was of much greater significance than the finding of individual bodies, which merely indicated that there had been exposure to asbestos dust.

Personal Observations. The following observations are based partly on Professor Stewart's collected material, partly on a reinvestigation of the cases which he had previously examined, and partly on a few new cases first seen during the first half of 1934. Thirty-eight individual cases have been studied, and a large number of specimens of sputum examined.

Of these cases 11 have died and in 10 the presence of asbestosis was confirmed postmortem. In 6 cases there was superimposed pulmonary tuberculosis, in 2 a terminal acute bronchitis and in 1 the proximate cause of death was influenza. In 1 case death followed pregnancy and parturition and in 1 (Case 14) an abdominal

operation. In this case no autopsy was obtained. Of the surviving cases, 2 are now acutely ill with pulmonary tuberculosis, 2 are doubtfully tuberculous, while 9 are apparently uncomplicated cases of pulmonary asbestosis of considerable and progressive severity. Four others present evidence of mild asbestosis. Adequate information is lacking in regard to 7 of the remaining 10 cases, while the other 3 are in excellent health. Of these, 2 are office employees and the third was employed in an asbestos factory only after the introduction of modern methods. In consequence she was exposed to a minimum amount of dust.

Detailed examination of these cases has been going on at varying intervals for a period of 5 years. Several have been receiving medical attention for indefinite periods and the sputum has been examined at intervals when conditions permitted. Patients with pulmonary asbestosis are extremely susceptible to chest colds and coughs, particularly so during the damp winter months. It is upon such occasions that the ever-present cough becomes productive and that sputum may be obtained for examination.

The best time to obtain a specimen is in the morning owing to the accumulation of mucus overnight. The type of sputum varies: usually in an uncomplicated case it is very thick and tenacious and when allowed to stand develops a very disagreeable odor. When tuberculosis is associated, pus and streaks of blood are not infrequently present. The consistency in many cases is not uniform; clear, thin, watery mucus, when present, tends to settle out from the underlying thick and stringlike portion.

In conjunction with this work complete clinical and radiologic examinations have been done wherever possible. In the developed disease dyspnea and cough are the ever-present and progressive symptoms. Physical signs are for the most part localized to the region of the lower chest. Roentgen ray examinations invariably confirm the findings on physical examination, and when taken at infrequent intervals illustrate a definite bilateral progressive, mainly basal, fibrosis, with characteristic signs of old pleurisy, hazy diaphragmatic margins, and so on. Complications in the nature of upper respiratory infections, bronchitis, bronchiectasis, empyema, pneumonia and especially tuberculosis, aggravate the symptoms to a notable degree, with greatly increased debilitation of the patient and evidence of right heart failure. In all cases the sputum has been examined for the presence of asbestos bodies (including clumps) and tubercle bacilli, and in a small group of 6 cases a special search for elastic tissue has been made.

Technique for Demonstration of Asbestos Bodies. The method originally suggested by Stewart and Haddow (Stewart, 1929) consisted in adding to selected portions of the sputum an equal quantity of antiformin. Following gentle agitation in a test tube and the addition of 4 or 5 times the volume of water, the mixture is placed in the incubator at 37° C. for some hours.

The supernatant fluid is now poured off and the last 10 to 15 cc. centrifuged for 5 or 10 minutes. The supernatant fluid is again poured off and the precipitate, by means of a very fine pipette, is placed on albuminized slides. The films are dried, fixed and washed, and mounted in Canada balsam.

Simson and Strachan (1931) suggested a direct method. Thick films of the mucoid portion of sputum were made and dried in a paraffin oven at 54° C. These were fixed with saturated mercuric chlorid solution and subsequently stained with hematoxylin and eosin. These workers concluded that "it was as easy to demonstrate bodies in the direct film as in the antiformin method" and recommended its use as showing both the cytology of the specimens and the intracellular development of the asbestos bodies.

Gloyne (1931) describes a method in which ammonium sulphate replaces the hematoxylin. After antiformin digestion and centrifugation the antiformin is pipetted off and replaced by 5% ammonium sulphid. The bodies as a result are colored black. The author recommends this method because it allows the minute details of the body to be clearly seen, while the central core of asbestos fiber can readily be observed extending between adjacent segments of the asbestos body.

Dr. Norah Schuster (Ellman, 1930–1931) uses the following simple wet method: The sputum is mixed with an equal quantity of 4% sodium hydroxid and left in the incubator until the mucus is dissolved (about 1 hour usually). Following centrifugation a wet film of the deposit is examined directly without staining.

The method used in the present study (Stewart, 1934) is substantially the same as the original.

Technique for Demonstration of Elastic Tissue. The sputum was prepared for staining by the method of Gentz and Bennet (1931). Three or 4 cc. of selected portions of sputum are placed in a centrifuge tube and 2 or 3 times this volume of 3% caustic potash is added. It is then shaken energetically until the mixture is homogeneous. Heat to the boiling point is now applied. Rapid cooling follows and the mixture is centrifuged for ½ to 1 minute. The supernatant fluid is poured off and the deposit placed on albuminized slides and allowed to dry. After being fixed with heat the films are carefully washed to remove the caustic potash.

Two methods of staining have been used for the demonstration of elastic fibers, one a modification of Barth's method (Calmette, 1928), the other a variant of Rappaport and Ellison's (1928–1929) modification of Weigert's stain. In Method I, Barth's orcein stain is heated to 55° C. and the slides immersed. They are kept at this temperature for from 1 to 2 hours, and are then washed in water, differentiated in acid alcohol (2 to 3% hydrochloric acid in 95% alcohol), washed again in water, dehydrated in absolute alcohol, cleared in xylol and mounted in Canada balsam. The elastic fibers are stained a dark reddish purple.

In Method II, the films are immersed in Weigert's stain, as prepared by Rappaport and Ellison, for a period of 20 minutes, following which they are washed in water, differentiated in acid alcohol (2 to 3% hydrochloric acid in 95% alcohol), washed again in water, dehydrated in absolute alcohol, cleared in xylol and mounted in balsam. Elastic fibers are stained a deep blue-black.

The relative merits of these two methods of staining are as follows: The stain as used in the Barth method is relatively easier to prepare, and once prepared can be used for an unlimited time, while the modified Weigert's stain, besides being far more difficult to prepare, tends to deteriorate much more quickly. On the other hand it stains elastic tissue in 20 minutes, whereas the modified Barth method takes from 1 to 2 hours. The final result is equally efficient and each can be used as best fitted to the individual laboratory.

TABLE 1.—LIST OF CASES.

Case No.	Sex and age (yrs.).	Duration of exposure to dust (yrs.); nature of work.	Interval since leaving employment (yrs.).	Interval since first exposure to dust (yrs.).	Clinical diagnosis at time of sputum examination.	Duration of exposure when sputum examined (yrs.).	Sputum. Bodies.	Sputum. Clumps.	Sputum. Tubercle bacilli.
1	F 25	4 Mattress making	2	6	Always subject to catarrh; Roentgen ray negative for both tuberculosis and asbestosis. No definite Roentgen ray evidence of asbestosis. Now, 2 years later, apparently in excellent health.	3 4	– –	– –	– –
2	M 34	3 Spinner	3	6	Very mild fibrosis; continuous dry hacking cough.	2	+	–	–
3	M 36	7 Office worker	Still empl.	7	Excellent health; no cough.	2	+	–	–
4	M 28	10 Office worker	Still empl.	10	Excellent health; no cough. Now, 5 years later, still in excellent health.	5	+	–	–
5	F 27	10 Spinner	Still empl.	10	Cold; cough; gastritis; thought to be due to asbestos dust; definite jaundice. Pulmonary asbestosis.	5 10	– +	– –	– –*
6	F 27	6 Teaser and corder	4	10	Definite progressive basal fibrosis.	9	+	–	–
7	M 30	9 Every dept.	½	10	Pulmonary tuberculosis superimposed on asbestosis. Confirmed postmortem 7 months later.	9½	++	+	+
8	M 45	9	4	13	Bilateral asbestosis with associated tuberculosis. Confirmed postmortem 1 year later.	12	++	+	–
9	M 37	13½ Associated with much dust	Still empl. clerk	14	Bilateral pulmonary asbestosis with suggested superadded tuberculous infiltration of upper zone of right lung.	14	++	+	–
10	M 46	12 White dust	3	15	No data. Died of pulmonary asbestosis with superimposed tuberculosis 3 years later; confirmed postmortem.	12	++	–	–
11	F 31	11 Mattress maker	3	16	Advanced pulmonary asbestosis, bronchitis and cardiac failure; confirmed postmortem.	16	++	+	–
12	F 31	15 Mattress maker	1	16	Progressive pulmonary asbestosis of moderate severity. Similar state.	15 16	+++ ++	+ –	– –
13	F 44	1	16	17	Bronchitis.	17	+	–	–
14	M 55	15 Spinner	1	16	Emphysema with dyspnea, cough and pain in abdomen. Very ill; cirrhosis of liver(?). Later laparotomy was done; death followed.	12 15	+++ +++	– –	– –
15	M 36	18 Foreman mattress maker	¼	18	Pulmonary tuberculosis and asbestosis. Confirmed by postmortem 1 year later.	17	++	–	+
16	M 43	6	12	18	Pulmonary asbestosis complicated by tuberculosis.	18	++	+	+*
17	M (?)	20 Spinner	..	..	(?) Tuberculosis plus asbestosis.	..	+	–	–
18	F 35	18 Mattress maker	3	21	Progressive pulmonary asbestosis with cardiac involvement. Died 1 year later following pregnancy and parturition.	20+	+	–	–
19	F 35	6 Mattress maker	16	22	Right-sided basal pleural thickening; dyspnea, cough; tubercle suspected; tuberculosis confirmed. Primary pulmonary asbestosis with superimposed active tuberculosis.	20 22	+++ +++	+ +	+ +
20	M 47	17 Mattress maker	2	22	Pulmonary asbestosis. Progressive pulmonary asbestosis.	19 22	++ ++	– +	– –*
21	F 45	6 Mattress maker	15	23	Cerebral softening; acute bronchitis and bronchopneumonia with associated asbestosis. Confirmed later, postmortem.	23	+	+	–
22	F 41	19 Mattress maker	4	23	Cough, dyspnea; evidence of basal fibrosis by Roentgen ray examination. Death from acute influenza 2 years later.	21	+	–	–

* Elastic tissue present (Cases 5, 16, 20).

TABLE 1.—LIST OF CASES—*Continued.*

Case No.	Sex and age (yrs.).	Duration of exposure to dust (yrs.); nature of work.	Interval since leaving employment (yrs.).	Interval since first exposure to dust (yrs.).	Clinical diagnosis at time of sputum examination.	Duration of exposure when sputum examined (yrs.).	Sputum.		
							Bodies.	Clumps.	Tubercle bacilli.
23	F	22	2	24	Mild pulmonary fibrosis.	18	+†	–	–
	40	Mattress maker			Progressive pulmonary asbestosis.	24	+	–	–
24	F	4	14	24	Pulmonary asbestosis with tuberculosis.	23	++	–	+
	37	Spinner			Asbestosis with extensive phthisis confirmed by postmortem 1 year later.				
25	F	16	9	25	Suggestion of pleural effusion.	22	+†	–	–
	44	Mattress maker			Progressive pulmonary asbestosis. Two years later, advanced asbestosis, dry cough.	23	+	–	–
26	F	13	10	26	Pulmonary asbestosis.	21	+	–	–
	39	Mattress maker			Uncomplicated pulmonary asbestosis of pronounced severity.	26‡	+	–	–
27	F	21	2	29	Progressive pulmonary asbestosis.	27	++	+	–
	46	Mattress maker			Uncomplicated pulmonary asbestosis.	29‡	++	+	–
28	M	30	Still empl.	30	Very severe cough, dyspnea; mild pulmonary asbestosis.	25	++	–	–
	63	Cashier			Pulmonary asbestosis and tuberculosis confirmed later postmortem.	30	++	–	++
29	M	35	Still empl.	35	General condition fairly good.	35	++	–	–
	55	Warehouse man							
30	F	31	4	35	Fairly advanced fibrosis (Roentgen ray examination).	26	++	–	–
	67	Mattress maker			Progressive uncomplicated pulmonary asbestosis.	31‡	++	–	–
31	M	50	..	50	Advanced pulmonary fibrosis.	50	+++	–	–
	63	Fiber rope dept.							

† Lung juice.
‡ Elastic tissue not present on repeated examinations (Cases 26, 27, 30).

Analysis of Cases. The present study includes 38 cases of asbestos workers of whom 31, where full details are available, are recorded in the preceding table. The cases have been arranged in accordance with the period of time that has passed since they first became exposed to asbestos dust, which in several cases is not equivalent to the actual duration of exposure plus the interval since leaving employment, since some were employed irregularly or were absent from work on account of childbirth, service overseas, etc.

Twenty-one of the cases are males and 17 females. The age at which they began working in an asbestos factory ranges from 13 to 39, average 21, but 17 of the 31 recorded in the table began work before the age of 21. The average duration of exposure is 15 years, with a range from as low as 1 up to 50 years. Tuberculosis was present in 8 cases, and in this group the average period of exposure was 9.2 years, as contrasted with 16 years in the non-tuberculous group. Case 28 is exceptional in that he was not really a worker in asbestos and he is therefore not included in the averages given.

Sputum Examination. *Asbestos bodies* have been present in every case with the exception of Case 1, a woman, aged 25, who was in contact with a minimum amount of dust as a mattress maker for

4 years, the whole period being subsequent to the abolition of the dry method of manufacture. She has always been subject to respiratory tract catarrh, which may have been a factor in preventing entry of dust to the lung alveoli. With two exceptions (Cases 1 and 5) bodies were demonstrated at every examination. In Case 5 the sputum was negative after 5 years' exposure but positive (a solitary body only) when examined after 10 years' exposure.

The number and type of bodies were most variable. Generally the large beaded or "weathered" type of bodies, deep brown in color and strongly iron-reacting, were most prevalent in cases where the interval since the onset of exposure had been long, including those where a long interval had elapsed since they were last employed in asbestos. Bodies recovered from those who had only been in this employment for a few years were smaller in size, paler in color and less strongly iron-reacting. It is clear that asbestos bodies in the lung slowly increase in size with the passage of time and become in consequence both darker in color and more strongly iron-reacting.

Clumps or groups of bodies were present in 10 of the cases. Five of these had tuberculosis, of whom 3 have died and the other 2 are critically ill. One of the remaining 5 cases is doubtfully tuberculous, 1 has died of pulmonary asbestosis with associated cardiac failure, while the remaining 3 are apparently cases of progressive uncomplicated asbestosis.

In 6 cases (Nos. 5, 16, 20, 26, 27 and 30) the sputum was examined for *elastic tissue* by the methods described and a positive result obtained in 3. In Case 5 a solitary "weather-beaten" asbestos body was discovered after 10 years' exposure, yet elastic tissue was present (Fig. 1). In Cases 26 and 30, bodies had been found on several former occasions but neither clumps nor tubercle bacilli; elastic tissue was absent from both. In Cases 20 and 27 clumps as well as single bodies had been found previously but no tubercle

LEGENDS FOR FIGS. 1 TO 7.

FIG. 1.—Case 5, F., age 25. Elastic tissue in sputum of asbestos worker. Ten years' exposure to asbestos dust. Only one "weather-beaten" body found, no clumps, no tubercle bacilli. × 300.

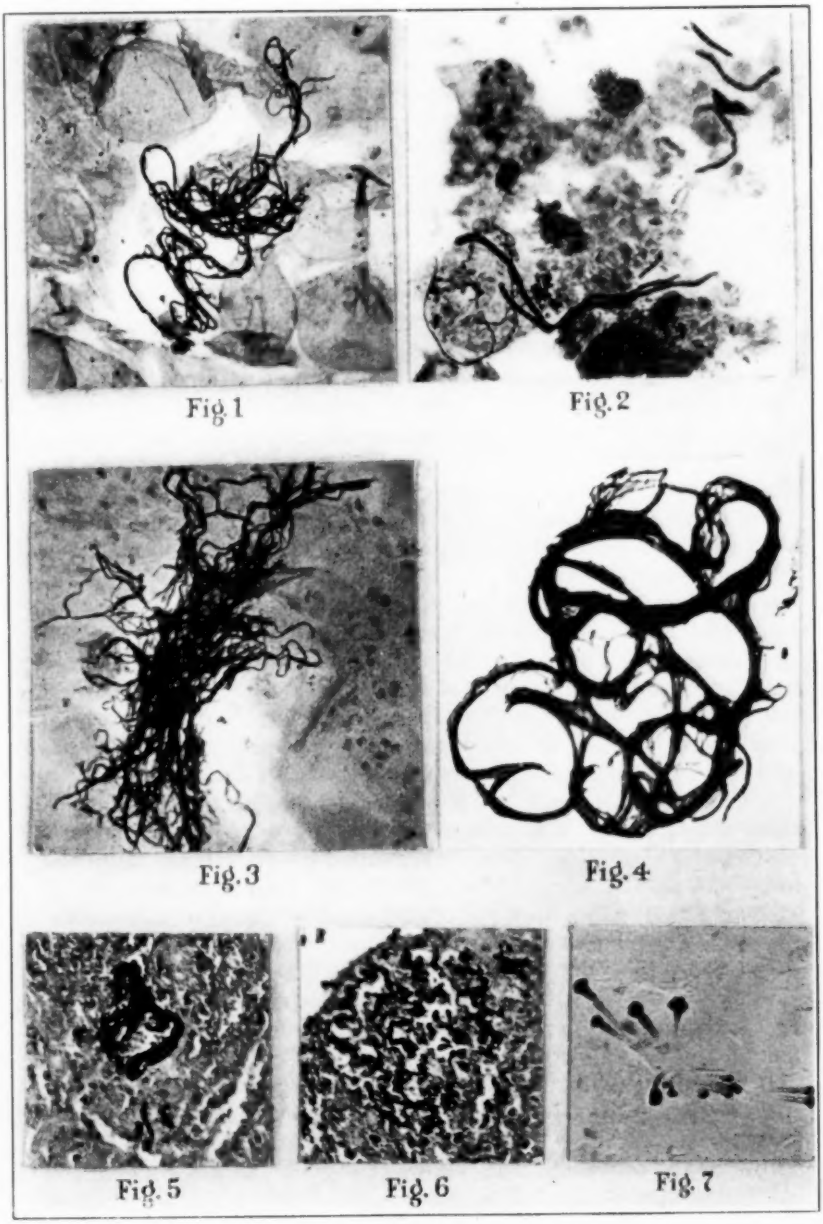
FIG. 2.—Case 20, M., age 47. Elastic tissue in sputum of asbestos worker. Twenty-two years since onset of exposure (duration 17 years). Asbestos bodies and clumps present, but no tubercle bacilli. × 300.

FIG. 3.—Case 16, M., age 43. Elastic tissue in case of asbestosis with tuberculosis. Eighteen years since onset of exposure (duration 6 years). Elastic fibers, asbestos bodies and clumps (Fig. 7) and tubercle bacilli all present. × 300.

FIG. 4.—Elastic tissue in sputum of a pure case of pulmonary tuberculosis. × 300.

FIGS. 5 and 6.—Case 28, M., age 63. Elastic tissue in caseous material in a phthisical cavity. Case of pulmonary tuberculosis superimposed upon asbestosis. Interval since onset of exposure 30 years. × 300.

FIG. 7.—Case 16. Small clump of asbestos bodies in sputum, from same case as Fig. 3. × 300.



FIGS. 1 TO 7.

bacilli; elastic tissue was demonstrated in Case 20 (Fig. 2). In Case 16, clumps, tubercle bacilli and elastic tissue were all present (Figs. 3 and 7). These results are summarized in Table 2.

TABLE 2.—CASES EXAMINED FOR ELASTIC TISSUE.

Case No.	Asbestos bodies.	Clumps.	Elastic tissue.	Tubercle bacilli.
5	+ (1)	−	+	−
16	+	+	+	+
20	+	+	+	−
26	+	−	−	−
27	+	+	−	−
30	+	−	−	−

Discussion. The findings here reported are for the most part in accordance with those of other workers and show that the mere presence of asbestos bodies in the sputum of an individual denotes nothing more than that he has at some time been in contact with asbestos dust. The actual number of bodies is likewise of little significance. If, however, they are consistently present in considerable numbers the possibilities are that either the individual has been in contact with large quantities of dust over a long period or there is some underlying pathologic condition of the lung, leading to gradual liberation of accumulated bodies. This is illustrated in Cases 14 and 19. In the former the sputum upon repeated examination showed large numbers of bodies, the individual in question having been associated at the time of examination and for 15 years previously with large quantities of dust. Case 19, on the other hand, also with numerous bodies on repeated examination, had only been directly exposed for a period of 6 years and had not been in contact with dust for 16 years at the time of examination. Clinically there was an associated tuberculosis.

The type of body present is of considerably greater significance than the number. The formation of asbestos bodies in the lung takes but a short time. They were found by Simson (1929) in the lungs of a patient who had been exposed for 2 months only, and by Stewart (1930) in a guinea pig after 3 months' exposure in an asbestos factory. Once formed, they can remain in the lung for an indefinite period. In a patient of Ellman's (1933) exposure was for 10 weeks only, and 5 years later bodies were recovered from the sputum. In Case 13 of this series, the patient had worked in asbestos for 1 year, and 17 years later bodies were still present in small numbers.

Reference has already been made to the "growth" or increase in size of these bodies, presumably by slow diffusion out of silicates from the central fiber and their interaction with constituents of the surrounding body fluids. It follows that bodies of large size in the sputum indicate that these have formed around fibers inhaled many years before. On the other hand, small, thin bodies, though doubtless of recent formation, are no indication that their central fibers have been recently inhaled. "Young" bodies may be encountered in sputum from persons who have had no opportunity

of inhaling dust for many years, and it is known that asbestos fibers may remain in the lung for long periods without necessarily becoming converted into "bodies" at all.

Another point of great importance is the so-called "weathering" of the asbestos body. Many of the old large bodies present a distinctly ragged or weather-beaten aspect, often consisting, as it were, of widely separated irregularly shaped beads strung on the fibrous core. There can be little doubt that this process is associated with solution and disintegration of "body" substance and accounts, in my opinion, for the interesting finding of Fowweather that the silica content of the fibrotic portion of the asbestos lung is much less in workers who have been away from dust for many years than in those recently or still in employment, even where the length of exposure has been the same. "Weathering" is probably a constant process in these cases, but may be accelerated by the occurrence of caseous or suppurative change.

The clump-like arrangement of bodies within the lung alveoli was observed from the very outset of detailed histologic studies (Stuart McDonald, 1927). When the presence of clumps in the sputum was first reported by Stewart, Tattersall and Haddow (1932) it was suggested that this finding was a clear indication of disintegration of lung tissue, whether by a process of simple suppurative bronchopneumonia or as a result of a secondary tuberculous infection. In either case it was regarded as being virtually diagnostic of an underlying asbestosis. In the present study, 10 cases in which clumps were present in the sputum tend to substantiate this view. Four of them suffered from superimposed tuberculosis. Two of these have died and the remaining 2 are now critically ill. One other patient in whose sputum a clump was demonstrated is considered as a probable case of superimposed pulmonary tuberculosis. Of the remaining 5 cases, 2 have died, 1 of cerebral softening, acute bronchitis and bronchopneumonia, the other of bronchitis and cardiac failure, both with underlying asbestosis. The remaining 3 are suffering with definite progressive pulmonary asbestosis, fully confirmed by clinical and radiologic examination.

While the presence of asbestos clumps in the sputum is probably indicative of lung destruction, the converse is by no means true, that is, the absence of asbestos clumps affords no assurance of pulmonary integrity. There are many cases in the present series in which there has been definite disintegration of the lung and yet no clumps have been demonstrated in the sputum. Other possible fallacies exist. More prolonged and more careful examination might have yielded a positive result, or roughness in handling may have caused the clumps to break up. Lastly and perhaps most important, the underlying pathologic condition in the lung may have led to chemical or physical dissolution of the clumplike arrangement so that when expectorated in the midst of caseous material or pus, the clumps may have disintegrated into their individual fibers.

Gardner and Cummings (1931) state that in guinea pigs tuberculous caseation causes the asbestos bodies present to lose their golden-yellow color; they also fail to give a Prussian blue reaction and later are apparently so completely disintegrated that not even a supporting fiber remains.

Elastic tissue in the sputum, irrespective of the underlying pathologic condition, has long been accepted as unequivocal evidence of lung disintegration. Rappaport (1929–1930) mentions that elastic tissue may appear in the sputum of patients who present only very mild signs of clinical activity. He refers to Durand, a French worker, who demonstrated elastic fibers in the sputum of tuberculous patients, both before and after the appearance of tubercle bacilli. The 3 cases of the present series in which elastic tissue has been demonstrated in the sputum illustrate several points of interest. In Case 5, the presence of the elastic fibers is difficult to explain. She had been exposed to asbestos dust, it is true, for the last 10 years, and during this time it is quite possible for a progressive pulmonary asbestosis to have developed. Yet only a solitary asbestos body was found on one occasion. There was no definite evidence of tuberculosis, but the possibility that this disease existed in an abacillary or prebacillary stage could not be excluded. In Case 20, the presence of elastic fibers is associated with a rapidly progressive form of uncomplicated pulmonary asbestosis. In Case 16, the presence of elastic tissue is associated with active tuberculosis and clearly indicates a state of definite disintegration. The underlying pulmonary lesion here is probably illustrated by Case 28, from which Figures 6 and 7 were obtained. These show, in sections of the lung, elastic tissue in the midst of caseous tuberculous material, in a similar form to that expectorated in Case 16.

A careful search for tubercle bacilli has been carried out in every sample of sputum obtained. Positive findings were present in 6 out of 8 cases of proven tuberculosis. The incidence of tuberculosis in this series is therefore 21%, exactly the same as that recorded by Wood and Gloyne (1931), but less than figure given by Ellman (1930–1931), 6 out of 17 cases. Bridge (1931) reports an incidence of 31.5% in fatal cases.

Conclusions. 1. The presence of asbestos bodies in the sputum is indicative merely of exposure to asbestos dust. If they are of large size it means that a long interval has elapsed since the onset of exposure.

2. The number of bodies in any given specimen is insignificant, but the presence of old and weathered bodies on repeated examinations strongly suggests that a definite pathologic process is in existence.

3. Clumps in the sputum are definite evidence of lung disintegration, but their absence does not mean that disintegration is not in process.

4. Elastic fibers are probably indicative of rapid lung destruction.

5. Elastic fibers may be present in the sputum in pure pulmonary asbestosis both with and without clumps, or in asbestosis with associated tuberculosis.

6. The routine examination of the sputum in cases of suspected pulmonary asbestosis is essential, as it plays a significant rôle in the clinical diagnosis.

I wish to express my sincere appreciation to Professor M. J. Stewart for the use of his personally collected material, his friendly criticism and able advice, under whose guidance this paper has been written, and to the British Medical Research Council for financial assistance.

I am also indebted to Dr. A. C. Haddow and Dr. N. Tattersall for the use of their clinical and radiological material, and to Mr. Lawson for his technical assistance.

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ACETYL-β-METHYLCHOLIN (MECHOLIN). OBSERVATIONS CONCERNING ITS ACTION ON THE BLOOD PRESSURE, SKIN TEMPERATURE AND THE HEART, AS EXHIBITED BY THE ELECTROCARDIOGRAM OF HYPERTENSIVE PATIENTS.

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Hunt and Taveau[1] were the first to prepare and determine many of the pharmacologic properties of acetyl-β-methylcholin. Major and Cline[2] have synthetized it ("mecholin") by a process which has made it available in quantity. Recently studies of its pharmacology

have also been carried out by Simonart,[3] and Comroe and Starr.[4] Starr, Elsom, and Reisinger,[5] have made clinical investigations of interest; especially their observation that mecholin is useful in the treatment of peripheral vascular disease, that it terminates attacks of tachycardia, and that it reduces the level of the blood pressure when taken by mouth. It has therefore seemed desirable to study the effect of mecholin on the heart as measured by the electrocardiograph, to learn whether it is of therapeutic importance in the treatment of hypertension in patients, and to ascertain its effect on the skin temperature.

Description of Response to Mecholin Subcutaneously Injected Into a Hypertensive Patient. Almost immediately after 25 mg. of mecholin* were injected subcutaneously the face began to flush and tears poured from the eyes. The pulse became more rapid and the flush deepened and extended progressively down over the chest and upper abdomen. Respiration became deep and slower. Beads of sweat then began to appear and collected until the patient was literally drenched. The blood pressure which had been 210/140 mm. Hg fell to 96/70 mm. Hg. The patient gave a few hacking coughs and complained of gripping pains in the epigastrium. She found difficulty in breathing and stated that her heart was pounding in an alarming fashion. Saliva drooled from her mouth and she felt choked. The flushing and perspiration extended down to her hands and feet but did not include them; rather they appeared cold and slightly bluish. Vomiting occurred and the reaction was immediately terminated by injection of atropin (gr. $\frac{1}{100}$). The patient then complained of being cold.

This describes a typical but severe reaction. Most of our studies have been conducted employing doses of 10 mg., which produces a relatively mild and not seriously uncomfortable effect. It is our impression that hypertensive individuals respond more actively than do normal ones to mecholin, but that old individuals, especially when suffering from arteriosclerosis, respond sluggishly.

Effect of Mecholin on the Mechanism of the Heart Beat (Electrocardiograph) and on the Size of the Heart. Electrocardiographic records were taken just before and at 2-minute intervals after the injection of mecholin. The most characteristic change observed after doses of 10 mg., though it did not occur in all subjects, was inversion of the *T* wave in all three leads. No change in *A–V* conduction time was noted in any of the records. The rate of the heart (Fig. 1) was always markedly increased. Atropin (gr. $\frac{1}{100}$) not only terminated the action of the mecholin but also appeared to cause the *T* wave to resume its upright position. Evidently the action of the drug is not primarily on the cardiac muscle. Mecholin given by mouth in dosages of 1 gm. produces no changes measurable

* We are very grateful to D. R. T. Major of the Laboratories of Pure Research (Merck & Co.) for a large supply of mecholin.

by the electrocardiograph. The records were taken at 30-minute intervals for a 2-hour period.

TABLE 1.—EFFECT OF MECHOLIN, SUBCUTANEOUSLY ADMINISTERED, ON THE HEART AS MEASURED BY ELECTROCARDIOGRAMS.

Patient.	Time.	Blood pressure.	Change in *T* wave.			Electrocardiogram conduction time.	*R* wave.	Other findings.
			T_1.	T_2.	T_3.			
Essential hypertension Dec. 15th	3.22	218/150	+	+	±	0.16	....	Left ventricular preponderance.
	3.24	Mecholin 10 mg.						
	3.26	140/70	+	+	−	0.16	R_3 low voltage	
	3.28	145/100	+	+	−	0.16	R_3 low voltage	
	3.29	170/110	−	+	−	0.16	R_3 low voltage	
Nov. 16th	10.30	196/128	+	+	+	0.15	....	Left ventricular preponderance.
	10.37	Mecholin 10 mg.						
	10.40	140/80	−	−	−			Ventricular preponderance absent.
	10.45	140/84						
	10.48	140/86	Same but rate more rapid					
	11.30	160/116						
Latent hemor. Bright's disease Nov. 20th	10.02	190/120	+	+	+	0.18		
	10.04	Mecholin 10 mg.						
	10.05	....	Same but pulse more rapid. *T* waves flattened.					
	10.06	120/70	−	−	−			
	10.08	144/102						
Essential hypertension	10.35	260/150	+	+	+	0.18	....	Left ventricular preponderance.
	10.36	Mecholin 10 mg.						
	10.37	Same but more rapid pulse						
	10.38	190/120						
	10.40	Same but lower voltage in S_3						
	10.41	210/130						
Hemor. Bright's disease Nov. 14th	10.58	158/106	+	+	−	0.21		Left ventricular preponderance.
	11.00	Mecholin 20 mg.						
	11.01	110/55						
	11.02	90/45	+	+	−	0.20	R_3 split	Rate more rapid.
	11.08	80/20	+	+	−	....	*U* wave	
	11.10	88/48						
	11.13	80/40						
	11.13	Atropin gr. 1/125						
	11.20	146/110						
Hemor. Bright's disease	9.32	204/132	+	+	+	0.15	Low voltage and split.	
	9.34	Mecholin 10 mg.						
	9.36	160/70						
	9.37	....	−	+	−	....	Higher voltage.	
	9.38	110/60	−	+	−			
	9.40	Atropin gr. 1/100						
	9.42	150/110	±	+	+	....	Low voltage and split.	
Hemor. Bright's disease	4.12	190/110	+	+	−	0.15	....	Left ventricular preponderance.
	4.14	Mecholin 15 mg.						
	4.15	100/60	+	+	0	0.18		
	4.16	Atropin gr. 1/100	−	−	−	0.17		
	4.17	108/65						
	4.23	Atropin gr. 1/100						
	4.24	150/110						
	4.25	....	±	±	−	0.18		

The size of the heart studied in Roentgen ray photographs, taken at minute intervals for a period of 5 minutes following injection, shows no striking change, although after 1 minute a definite but small decrease followed by a slight increase was noted. The cardiac

(1) (2) (3)

FIG. 1.—Inversion of the *T* wave following mecholin injection (Patient No. 3). (1) Control period (B. P. = 190/120); (2) 2 minutes after 10 mg. mecholin subcutaneously; B. P. = 120/70; (3) 4 minutes after mecholin; B. P. = 144/102.

shadow shows these changes* in size: Control, 122.2 sq. cm.; 1 min. after mecholin, 110.2 sq. cm.; 2 min., 120.7 sq. cm.; 3 min., 136.6 sq. cm.; 4 min., 130.6 sq. cm.; 5 min., 135.2 sq. cm.

Effect of Mecholin Administered by Mouth on the Level of the Blood Pressure. Mecholin in doses of 0.9 gm. administered by mouth decreases the blood pressure slightly in hypertensive subjects. The action is variable, in some patients no reduction occurred.

TABLE 2.—EFFECT OF MECHOLIN TAKEN BY MOUTH.

Patient.	Diagnosis.	Time.	Blood pressure.	Pulse.
		2.35	148/100	82
		2.40	142/102	84
		2.45	142/100	82
		2.46	Mecholin 0.4 gm. given	
	Hemorrhagic	2.56	142/86	82
Conlin	Bright's	3.06	140/96	84
	disease	3.20	142/90	80
		3.30	142/94	88
		3.45	144/94	90
		4.00	148/94	88
		5.25	148/96	88
		9.30	160/104	74
		9.40	164/106	76
		9.50	162/104	74
Gordon	Essential	9.55	Mecholin 0.9 gm. given	
	hypertension	10.05	154/104	72
		10.15	110/90	70
		10.25	134/88	68
		10.40	160/110	70
		11.25	170/104	78

Mecholin has been given to 2 patients suffering from essential hypertension (blood pressure: systolic 220, diastolic 130 mm. Hg; and systolic 260, diastolic 150 respectively) and in 2 with hypertension resulting from hemorrhagic Bright's disease (blood pressure: systolic 156, diastolic 102; and systolic 160, diastolic 110 respectively). They had remained in bed for several months and the level of the blood pressure had become stationary. They were well accustomed to experimental procedures. The measurements of the pressure were ordinarily made 1½ hours after the first dose of mecholin. The administration of amounts of mecholin up to 2 gm. (divided into 3 doses) had no effect on the level of their average blood pressure. Four grams daily (divided into 3 doses) were given to 1 of the patients for a period of 4 days, without effect. Large doses may cause transient reductions but the average level remains unchanged in the hypertensive subject.

The Effect of Mecholin on the Skin Temperature of Hypertensive Patients. The skin of the face and trunk when mecholin was administered subcutaneously, exhibited marked vasodilatation, but the hands and feet usually remained uninvolved. It seemed

* The area, traced on paper, is measured with a planimeter.

desirable therefore to repeat this observation and to measure the temperature of the skin.*

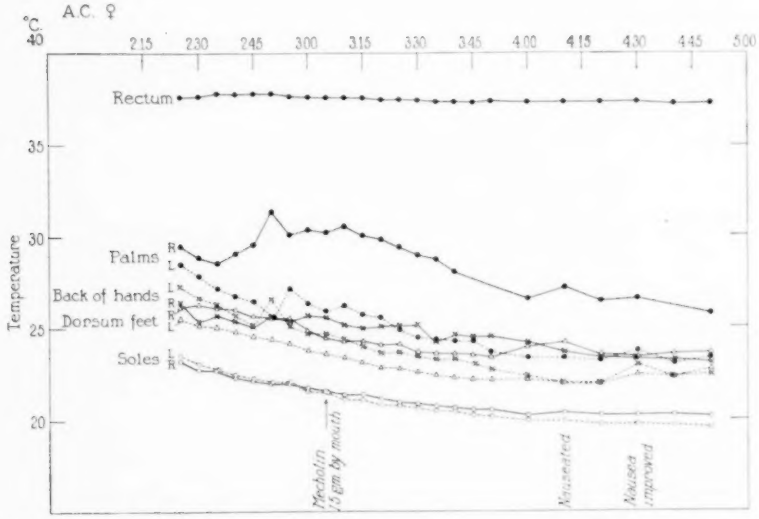

CHART I.—The effect of mecholin administered by mouth on skin temperature of hypertensive patients.

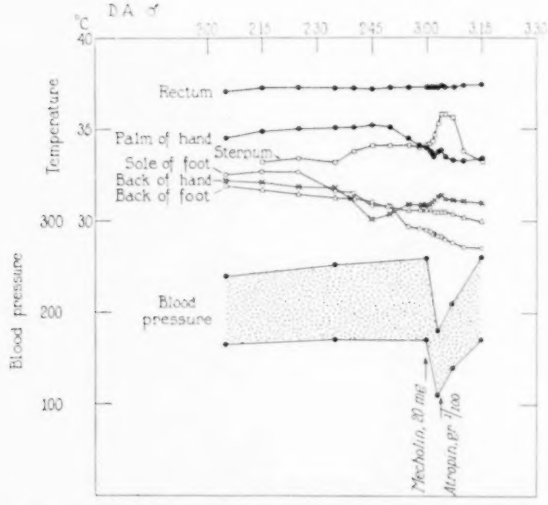

CHART II.—The effect of intramuscular injection of mecholin on skin temperature of hypertensive patients.

* These experiments were performed by Dr. J. Murray Steele. Dr. Steele will describe his modification of the Benedict thermocouple later.

Modified Benedict multiple thermocouples were employed for the purpose, placed on the chest, hands, feet, and in the rectum. The temperature of the room was constant, the normal fluctuations in the temperature of the skin were first recorded. Mecholin 10 to 15 mg. was then administered subcutaneously. The superficial vessels of the face and thorax dilated maximally. A corresponding rise in temperature occurred. The skin of the palms and backs of the hands, however, as well as of the dorsal and plantar surfaces of the feet, exhibited slight if any significant change. Oral administration also appeared to have no significant effect.

Discussion. One cannot but be impressed by the resemblance of the reaction to mecholin to that following the injection of pituitrin and pilocarpin into the cerebral ventricles. Cushing[6] observed that the injection of 1 cc. of pituitrin promptly caused intense flushing, profuse perspiration, lachrymation, retching and vomiting, salivation, marked fall in body temperature, coincidental lowering of the basal metabolic rate. These reactions occur in the absence of significant pupillary change, pilomotor action or stimulation of the lower bowel. The response to pilocarpin was similar except that (1) more marked vagal effect was noted with continued retching and vomiting and (2) the fall in body temperature was more marked and enduring.

These results suggest that when these drugs are introduced into the cerebral ventricles they do not act on the periphery through the medium of the circulating blood but depend for their action on impulses which travel from higher centers by way of the peripheral nerves. The reactions are similar to those following stimulation of the parasympathetic centers in the hypothalamus. They resemble furthermore attacks observed by Penfield[7] in a patient suffering from what he has described as "diencephalic autonomic epilepsy." Sudden vasodilatation of the skin area supplied by the cervical sympathetic chain occurred at the initiation of the attacks. This was followed by lachrymation, diaphoresis, salivation, retardation of respiratory rate and rarely loss of consciousness. The irritative source of the attacks was an encapsulated tumor which periodically pressed on the thalamus of both sides. This syndrome differs from that following mecholin in that the blood pressure rises sharply while in the latter the pressure falls precipitously.

In certain respects the reaction to mecholin differs from that usually observed following certain types of stimulation of the hypothalamic centers.[8] The first difference already mentioned lies in the fact that the blood pressure falls after mecholin administration, whereas ordinarily a rise is noted following stimulation of the hypothalamus. Vasodilatation is, however, the more usual parasympathetic and vasoconstriction the sympathetic reaction. To what extent the central mechanism is involved in vasodilatation is unknown but it seems certain that it plays an important part.

TABLE 3.—COMPARISON OF THE SIGNS AND SYMPTOMS RESULTING FROM MECHOLIN ADMINISTRATION WITH THOSE RESULTING FROM STIMULATION OF THE HYPOTHALAMIC CENTERS.

Pituitrin intraventricular.	Pilocarpin intraventricular.	Histamin intraventricular.	Stimulation of "parasympathetic centers."	Diencephalic epilepsy.	Mecholin intramuscular.
Slight rise in blood pressure	Slight rise in blood pressure	No change	Uncertain	Marked rise in blood pressure	Fall in blood pressure
Nausea	Nausea, vomiting	Nausea	Nausea, vomiting	.....	Nausea, vomiting
Marked flush	Marked flush	No flush	Marked flush	Marked flush	Marked flush
Perspiration	Perspiration	Slight perspiration	Perspiration	Perspiration	Perspiration
Lachrymation	Lachrymation	No lachrymation	Lachrymation	Lachrymation	Lachrymation
Salivation	Salivation	No salivation	Salivation	Salivation	Salivation
Temp. fall	Temp. fall	Sl. temp. fall	Temp. fall	Temp. fall	Temp. fall
Sl. slowing of pulse	Sl. slowing of pulse	No change in pulse	Slowing of pulse	Increased pulse rate	Increased pulse rate
No change in pupillary size	No change in pupillary size	.....	Constriction of pupil	Dilatation or contraction of pupil	No consistent change in pupil
Counteracted by atropin and tribromethanol	Counteracted by atropin	.....	.....	.....	Counteracted by atropin
Fall in basal metabolism	No m'rk'd change in basal metabolism	Slight rise	Decrease in basal metabolism		
.....	.....	Severe headache	.....	.....	No headache

A second point concerns the pulse rate. Parasympathetic stimulation usually leads to slowing of the heart rate but with mecholin this result is either transient or is not observed at all. It is possible that fall in blood pressure stimulates the sympathetic system reflexly enough to overcome the parasympathetic effect or does so directly. That the vagus nerves are stimulated, however, and not the muscle, may be surmised from the fact that inversion of the *T* waves in the electrocardiogram disappears on injection of atropin.

The peripheral dilatation of the bloodvessels is a matter of especial interest. It is first observed in the face, spreads down the neck, over the chest, but usually does not extend much below the umbilicus. The upper arms are involved and the legs to a much smaller degree. The feet and hands exhibit slight and transient flushing, but at times appear cyanotic. Active perspiration occurs approximately in the same areas as flushing and parallels its intensity. The reaction is striking; intensely red, perspiring faces and necks, distal portions of hands and feet often dry and dusky. It resembles that following the administration of amyl nitrite. Amyl nitrite, as Filehne[9] showed many years ago, produces dilatation by acting on certain centers in the brain, for when the vessels from the brain are clamped, no dilatation of the vessels of the rabbits' ears occurs, although the blood in the ears contains the drug. Conversely, when the circulation is intact and amyl nitrite is present in the cerebral blood, dilatation of the ear vessels occurs even if the ear is perfused with blood from another source free of amyl nitrite.

Mecholin like cholin acts also on the peripheral portion of the vascular bed. Decerebration of etherized cats does not abolish

the muscarin-like action. The fall in pressure is indeed often greater than before. But such experiments on anesthetized animals are not comparable to those on man.

Mecholin when injected subcutaneously into man seems then to have a powerful stimulating effect on the cerebral parasympathetic centers, presumably those in the anterior group of nuclei of the diencephalon—Cushing's "neurohypophyseal mechanism," which accounts for its ability to simulate so closely the signs and symptoms which arise either from direct electrical stimulation, from stimulation by the intraventricular injection of drugs, or from stimulation due to irritation by tumors. It is possible that the premotor area of the cerebral cortex also forms a part of the stimulated area. Recent data of Kennard[10] indicate that this area directly influences the autonomic nervous system and in particular the vasomotor mechanism.

The fact that dilatation of the bloodvessels occurs to a slight extent only in the hands and feet is a disappointment from the viewpoint of therapeutics. The rise in temperature is inconsequential and does not lead to the belief that marked therapeutic benefit can be derived from its administration. Starr has observed encouraging results from its use in Raynaud's disease, however. The fact that no marked changes occurred in the temperature of the skin of our patients suffering from arterial hypertension should not discourage its thorough clinical trial, as Starr recommends.

It is surprising to discover that the reaction to mecholin simulates an exaggerated blush. Heightened beating of the heart, flushing of the skin, drenching perspiration, the Rabelaisian effect of fright upon the bowel, the secretion by the lachrymal gland, all these are prominent characters in natural emotion. Mecholin induces this expression of the emotions without being accompanied by the emotions themselves. Evidently processes identified with the expression of emotions are secondary to or dependent on the behavior of the vascular and visceral organs and exist or can be called into existence without the need, as James, Lange and Sergi thought, of experiencing the emotion itself.

Conclusions. 1. Mecholin (acetyl-β-methylcholin), administered subcutaneously, greatly increases the temperature of the skin of the face and trunk of patients suffering from arterial hypertension; the hands and feet usually remain almost unaffected. Administered by mouth it fails to have this action.

2. Doses of 4 gm. taken by mouth have either no effect on the average blood pressure, or a slight one only.

3. When administered subcutaneously, mecholin usually causes inversion of the *T* waves of the electrocardiogram; this effect may be abolished by injecting atropin. Except for increasing the rate no other characteristic action of mecholin on the heart, as observed in the electrocardiograph, was seen. The size of the heart may first be

decreased and then increased briefly, the increase occurring when the level of the blood pressure has fallen markedly.

4. Comparison of the clinical phenomena due to injection of mecholin with those observed in patients suffering from diencephalic epilepsy, or in patients in whom pituitrin or pilocarpin had been injected into the cerebral ventricles, demonstrates a striking similarity between them. It has been suggested that many of the effects of mecholin are due to stimulation of the diencephalic parasympathetic centers, and possibly the premotor area of the cerebral cortex.

5. Mecholin causes most of the prominent corporal characters in the play of natural emotions to appear without being accompanied by the psychical counterpart itself.

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SO-CALLED HEMORRHAGIC ENCEPHALITIS AND MYELITIS SECONDARY TO INTRAVENOUS ARSPHENAMINS.*†

Based on a Review of 158 Cases.

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Central nervous symptoms secondary to the intravenous administration of arsphenamin were first reported in 1911 (Almkvist,[1] Fischer,[2] Kannengiesser[3]). More clearly to define this clinical picture and its prognosis, as well as to offer some facts about its

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etiology, prophylaxis and medical and surgical therapy, we have analyzed 155 cases from the literature and added 3 personally observed cases. In this analysis all questionable and borderline cases have been eliminated. There were 146 cases of encephalitis, [1–112] 8 of myelitis[113–120] and 4 of encephalomyelitis.[121–123] The meninges were involved in 33 cases, 30 being examples of meningoencephalitis, 2 of meningomyelitis and 1 of meningoencephalomyelitis. There were 120 deaths (a mortality of 76%), with 98 autopsies. In spite of this high mortality, these reactions occur infrequently, and for this reason one should not be influenced against the proper use of arsphenamins. Statistical studies indicate these reactions occur once in every 6500 cases, and once in every 36,000 injections. A multiplicity of terms has been used to describe this syndrome, such as cerebral purpura, serous apoplexy, hemorrhagic encephalitis, medullary perivascular necroses, toxic myelopathy and toxic myelitis.

TABLE 1.—TOXIC REACTIONS.

	No. of cases.	Injections.	Complications.	Deaths.
German, 1914[10]	74,018	288,942	642	56
German, 1917[10]	265,168	268,946	..	70
Cologne, 1920[125]	...	225,780	..	12
Civil England[10]	77,645	298,011	77	10
British Military Hosp.[10]	4,887	39,036	126	3
British Military Hosp.[10]	18,500	125,000	250	10
U. S. Navy, 1925–29[76–80]	16,075	257,789	282	20
Total	456,293	1,503,504	1377	181

The above statistics show that (omitting the second and third series) 191,125 patients receiving 1,108,778 injections of arsphenamin compounds had 1377 complications. One complication occurred in every 129 cases and in every 804 injections. One death occurred in every 2699 cases and in every 14,384 injections. Of this total number of deaths, about 50% were due to central nervous system lesions. There was approximately 1 death secondary to central nervous system involvement in every 5398 cases, and in every 28,768 injections. Of the remaining 50% of deaths, most were caused by exfoliating dermatitis and acute yellow atrophy of the liver; in rarer instances, by acute hemorrhagic nephritis, ulcerative enteritis and aplastic anemia.

Hemorrhagic encephalitis was first described by Rosenfeld,[126] in 1903. In 1905, a more thorough pathologic investigation was carried out by Schmidt,[127] who substituted the term "brain purpura." In 1913, Oeller,[128] attacked the term "hemorrhagic encephalitis." Alpers,[129] who reviewed the subject in 1928, believed that hemorrhagic encephalitis was a poor term because the hemorrhage was not an important part of the process, and it was not inflammatory, as the term "encephalitis" would imply. "Brain purpura"

was also inadequate because the pathology was not a purpura, but merely a purpuric rash. "Serous apoplexy" was not a good term because it did not explain the picture in all cases. He suggested the term "medullary perivascular necroses." The foci of hemorrhagic encephalitis have been reported in association with numerous other conditions, such as phosgene or carbon monoxid poisoning, grippe, pneumonia, tuberculous meningitis, malaria, typhus fever, cerebral trauma, pernicious anemia, secondary anemia, erythema multiforme, psoriasis, scurvy, cerebral thrombosis or embolism and meningovascular syphilis, or secondary to circulatory disturbance caused by hemorrhage, thrombosis and tumor.

Case Abstracts. Case 1.—A male, aged 29, complained of sore throat and painful, swollen cervical lymph glands, April 10, 1932. His past and family histories were negative. Two days later, a diagnosis of Vincent's angina and acute cervical adenitis was made, and he was given 0.15 gm. of neoarsphenamin intravenously without any reaction. On the 4th day after admission to hospital he was given 0.3 gm. of neoarsphenamin intravenously. On the 6th day he developed a hemorrhagic nephritis, and on the 7th day, an intense erythema of the skin of the entire body. On the 8th day the patient complained of a headache, vomited, became disoriented, irrational and comatose. He developed generalized convulsions and had a complete loss of sphincter control. Temperature range was 97.6° to 104.6° F. Pulse and blood pressure within normal limits. Neurologic examination on the 12th day revealed a stiff neck, bilateral Babinski, positive Kernig, abdominal reflexes were absent and deep reflexes normal. Pupils were contracted and did not react to light. Fundus vessels were congested. *Laboratory reports:* Urine contained albumin, numerous red and white blood cells and many hyaline and granular casts. White blood cells ranged from 6500 (38.5% neutrophils) to 24,000 (65% neutrophils). The blood Wassermann test was negative. The blood non-protein nitrogen varied from 43 to 49 mg. per 100 cc. Spinal fluid on the 12th and 13th days showed increased pressure, otherwise negative. Treatment was used for the Vincent infection, hot Epsom salt packs for the swollen lymph glands, morphin and codein, allonal and sodium amytal as analgesics and sedatives. Further treatment: 10 cc. of 10% sodium thiosulphate intravenously, 3 times daily, and 50 cc. of 50% glucose in saline intravenously, 3 times daily, normal saline hypodermoclysis, 1% glucose solution per rectum and 3 lumbar punctures. *Course:* On the 14th day the patient partially recovered consciousness and recognized objects. He improved steadily, and on the 16th day he regained full consciousness. On the 22d day he had entirely recovered.

Case 2.—A male, aged 35, complained of headaches, nausea and vomiting on March 30, 1933. His past and family histories were negative. The patient had received 4 doses of arsphenamin at weekly intervals for a skin eruption, the exact amount not ascertainable. On the day after the 4th dose the patient developed headache, with nausea and vomiting, and finally lapsed into a state of coma, remaining so for approximately 48 hours. The 3d day he developed a papular rash. He was seen on the 4th day. Neurologic examination revealed the patient in a stuporous condition; he could be aroused but quickly lapsed into unconsciousness. The pupils were slightly irregular, there was a failure of convergence and a lateral nystagmus on looking to the right. There was some difficulty in his upward gaze and a slight weakness of the right arm. Abdominal, cremasteric, patellar and Achilles reflexes were absent. *Laboratory reports:* Leukocytes, 4100;

neutrophils, 84.5%; hemoglobin, 90%; erythrocytes, 5,168,000. Urine, albumin present; on 4th day, positive for bile pigment. Spinal puncture, clear colorless fluid; pressure, 190 mm.; cells, 7 per c.mm.; globulin, slight increase; sugar, 74 mg. per 100 cc. Wassermann test negative. Under dehydration therapy, consisting of limitation of fluids and 50 cc. of 50% glucose intravenously, every 3 hours, and sodium thiosulphate, the 2d day following these injections his headache was entirely absent and he was perfectly conscious. Several days later he developed hepatitis with jaundice and evidence of acute nephritis as indicated by the red cells in the urine. Within 2 weeks he had entirely recovered and left the hospital.

TABLE 2.—INCIDENCE OF DISEASES TREATED WITH ARSPHENAMINS.

	No. of cases.	Percentage.
Syphilis	135	93
Vincent's angina	1	1
Pneumonia	1	1
Psoriasis	1	1
Skin eruption	1	1
Not stated	7	3
Total	146	

The occurrence of these reactions in non-luetic cases readily rules out the theories that attempt to place their occurrence upon a luetic basis.

TABLE 3.—AGE INCIDENCE.

Year.	No. of cases.	Percentage.
1 to 9	3	2.0
10 to 19	18	12.0
20 to 29	59	40.0
30 to 39	25	17.0
40 to 49	10	5.0
50 to 59	2	1.0
Not stated	28	22.5
60 to 70	1	0.5
Total	146	

The prevalence of this reaction in the third and fourth decade is without doubt due to the prevalence of syphilis during this period.

TABLE 4.—SEX INCIDENCE.

	No. of cases.	Percentage.
Males	89	60
Females	44	30
Not stated	13	10
Total	146	

Little emphasis need be placed on the predominance of these reactions in males, as we may assume males are more frequently afflicted with syphilis.

TABLE 5.—TOTAL DOSAGE OF ARSPHENAMINS USED BEFORE ONSET OF SYMPTOMS.

	No. of cases.	Percentage.
0.05 to 1.1 grams	78	53
1.10 to 2.1 "	44	30
2.10 to 5.6 "	17	11
Not stated "	7	6
Total	146	

When these toxic reactions were first described, it was the opinion that the dose of arsphenamin was too high, and for this reason smaller doses were recommended. Table 5 clearly demonstrates the falsity of this opinion and also that the quantity of the arsphenamin injected is not in any way related to the occurrence of symptoms.

TABLE 6.—NUMBER OF DOSES GIVEN BEFORE ONSET OF TOXIC SYMPTOMS.

	No. of cases.	Percentage.
1	19	13.0
2	72	50.0
3	23	15.0
4 to 9	26	17.0
9 to 15	1	0.5
Not stated	5	4.5
Total	146	

In 50% of the cases, hemorrhagic encephalitis followed the second injection. The significance of this fact we are unable to state.

TABLE 7.—TIME OF ONSET OF SYMPTOMS AFTER LAST DOSE.

	No. of cases.	Percentage.
Not given	42	31.0
1 to 12 hrs.	13	9.0
12 to 24 "	24	16.0
24 to 38 "	22	15.0
48 to 72 "	21	14.0
72 to 144 "	16	11.0
7 days	1	0.5
9 "	1	0.5
10 "	1	0.5
12 "	1	0.5
21 "	1	0.5
56 "	2	1.0
70 "	1	0.5
Total	146	

These reactions occur more frequently within the first three days after injection.

Hemorrhagic encephalitis in certain cases is so rapidly fatal that therapy is of no avail. In approximately 20% of the cases, death occurred within the first 24 hours. The time of death in the re-

maining cases varied from 2 to 35 days, thus the importance of an early diagnosis cannot be overemphasized.

TABLE 8.—TIME OF DEATH AFTER ONSET OF TOXIC SYMPTOMS.

	No. of cases.	Percentage.
1 day	23	20
2 days	18	15
3 "	15	13
4 "	4	4
5 "	1	1
6 "	4	3
7 "	2	2
8 "	1	1
35 "	1	1
Not stated	45	40
Total	114	

TABLE 9.—SYMPTOMS (146 CASES).

	No. of cases.	Percentage.
Headaches	58	40
Vomiting	55	38
Nervousness	14	9
Chills	12	9
Dizziness	10	8

It may be noted that headache, vomiting, chills, nervousness and dizziness occurred in the majority of these cases, whereas the following group of symptoms occurred in less than 5%: Perspiration, backache, fatigue, numbness, aphonia, dyspnea, dysphagia, photophobia, anorexia, hiccough, cough, body pains, diarrhea and diplopia. These predominating symptoms of headache, vomiting, dizziness are characteristic of increased intracranial pressure.

TABLE 10.—PHYSICAL SIGNS.

	No. of cases.	Percentage.
Fever	61	41
Respiratory changes	28	19
Cyanosis	26	17
Pulse changes	24	16

The physical signs are primarily: Increased temperature, pulse and respiratory changes and cyanosis, all indicative of toxic reaction. In addition to these symptoms, and occurring in less than 5% of the cases, are oliguria, anuria, skin rash, flushing of the skin, icterus and enlargement of the lymph glands. In all probability, fever occurred in more than 41% of the cases. Many of the records failed to mention the temperature status. Respiratory changes consisted of Cheyne-Stokes breathing, rapid respiration or paralysis.

Of the 146 patients, 80% had convulsions; 79% of them were unconscious. In a lesser degree, the various eye changes occurred which consisted of involvement of the 3d, 4th, 6th and 8th cranial

nerves. Hyperactive, hypoactive, absent and pathologic reflexes occurred in 30%. Meningeal signs, such as opisthotonos and rigidity of the neck, took place in approximately 13%. Such symptoms as generalized body rigidity, staggering gait, sensory disturbance, chewing movements, fibrillary tremors, excessive salivation and aphasia were reported. Mental disturbances consisting of delirium, disorientation as to time, place and person are found in less than 50%.

TABLE 11.—NEUROLOGIC SIGNS.

	No. of cases.	Percentage.
Convulsions	117	80
Unconsciousness	116	79
Pupillary and extraocular muscle changes	58	39
Reflex changes	45	30
Loss of sphincter control	32	21
Mental disturbance	29	20
Hemiparalysis of face, arms, legs	24	16
Rigidity of neck	19	13

TABLE 12.—LABORATORY STUDIES.

	No. of cases.	Percentage.
Laboratory work not stated	60	41
Laboratory work stated	86	59
Urine examinations reported	47	
Acute nephritis	17	35
Albumin	6	11
Normal	24	54
Lumbar puncture	39	
Pressure normal	6	16
Pressure increased	25	63
Not stated	8	21
Globulin increased	23	58
Red cells	10	26
White cells	24	63
Negative Wassermann	7	16

Of the 86 cases with laboratory data, 46% showed evidence of renal trouble—an indication of the diffuse nature of the lesion. The increase in spinal fluid pressure in 63% of 39 cases indicates that an increase of intracranial pressure is a salient feature of this disease. Subarachnoid hemorrhage was definitely indicated in 26% of the cases.

Myelitis. Toxic myelitis or myelopathy[115] without any demonstrable involvement of the brain is extremely rare. In the 22 cases of cord involvement that we have been able to collect from the literature, 8 had myelitis and 4 encephalomyelitis; 1 of the latter we have reported. In 11 cases of encephalitis, cord involvement occurred as a pathologic finding without clinical symptoms. The first case of myelitis following the intravenous injection of arsphenamin compounds was reported in 1911.[115] In this country Newmark[130] and Vecki[131] reported the first case (1911) of myelitis following the use of arsphenamin intramuscularly. Davidson and Kerschner[132]

feel that the term "myelitis" is very often employed to designate cases of diffuse non-systemic disease of the spinal cord in which the pathologic process bears no relation to infection, but is due to toxins, avitaminosis, vascular disease, trauma or compression. Many cases of so-called infectious myelitis are not cases of myelitis but represent a primary condition of the meninges or vessels with secondary changes in the cord which ultimately lead to myelomalacia. They believe that the term myelitis should be limited to inflammatory lesions of the cord and not degenerative. They prefer the term "toxic myelopathy" for the latter.

TABLE 13.—ANALYSIS OF DATA ON 8 CASES OF MYELITIS.

Author.	Sex.	Age.	Doses.	Total dose.	Onset of symp. after last inj., days.	Salient neurologic signs.	Treatment.	Outcome.	Lues.	Autopsy.
Zalkan[112]	M	24	2	1 5	1	Flaccid level lesion	Not stated	Not stated	Yes	
Bayet[113]	F	27	1	3 3	6	Level lesion, spastic	Not stated	Death, 6 mos.	Yes	Yes.
Chiari[114]	M	35	2	1 0	13	Level lesion, ascend.	...	Death, 17 days	Yes	Yes.
Fleischmann[115]	..	..	2	0 8	4	Level lesion, spastic	Hg; iod.	Slight improv.	Yes	
Juliusberg and Oppenheim[116]	..	15	1	0 2	6	Level lesion; men. signs.	Not stated	Not stated	Cong.	Yes.
Pechin[117]	M	35	3	..	1	Level lesion, flaccid	Novarsbenz. prog. 7 mo.	Comp. recov.	Yes	
Pinard[118]	M	23	1	1 8	2	Level lesion, flaccid	Not stated	Death, 2 wks.	Yes	Yes.
Scott and Reinhart[119]	M	..	1	0 6	8	Level lesion, spastic	Not stated	Persist.	No	

Inasmuch as we have only 8 cases of myelitis, 5.4% of all central nervous system cases, a statistical study would be of little value, but a table would serve to emphasize certain outstanding features of this condition. A small percentage of these cases had a rash or jaundice before onset of neurologic symptoms. In regard to sex, age, number of doses and total dosage, as well as the time of onset of symptoms after the last dose, those cases that develop a myelitis correspond to those that develop an encephalitis. The spinal cord lesion is one of massive involvement, usually ascending in type and either spastic or flaccid. In these 8 cases, only 1 made a complete recovery and, peculiarly enough, this case was given increasing doses of novarsenobenzol. Case 8 had a syphilophobia[119] and, in spite of all serologic studies being negative, demanded antiluetic therapy. Only 3 of this series came to complete autopsy, and the results of these are reported in detail in the original articles. The case reported by Newmark[130] and Vecki[131] following intramuscular arsphenamin also came to autopsy. The pathologic findings of the cases receiving intramuscular injections were the same.

In this series of 158 cases, there are 4 which manifest a combination of the clinical picture of an encephalitis and myelitis. This is 2.5% of total central nervous system cases. One of these cases, directly observed by us, is reported in detail.

Encephalomyelitis. CASE 3.—A male, aged 27, complained of sore throat, February 12, 1931. Past and family histories negative. Examination showed an acute ulcerative tonsillitis and smears revealed Vincent's organisms. He was given 0.15 gm. of neoarsphenamin intravenously. The 3d day, he developed retention of urine and was constipated. On the 6th day he noticed a peculiar abnormal sensation throughout his trunk and limbs. In the afternoon he received 0.15 gm. of neoarsphenamin intravenously. That night he had a fever, chills and hallucinations. On the 8th day he could not move his legs and had a generalized hypesthesia, and pain in the lumbar region that ascended to the thoracic region. On the 10th day he noticed weakness of the right arm and paresthesias in both hands. That afternoon the respirations became labored and the skin cyanotic. On the 12th day a lumbar puncture was performed, and in 24 hours the respiration improved. At this time he was seen in consultation. During the next 10 weeks he had involuntary urine and stools, and paraplegia of both legs; deep tendon reflexes of the arms active. Patellar and Achilles reflexes absent. There was a complete loss of sensation below the level of the 8th thoracic vertebra. Above the level of the 1st thoracic vertebra sensation was diminished. The temperature ranged from 98° to 102° F.; pulse, from 60 to 120; respirations, from 10 to 40. The blood Wassermann test was negative. The urine showed albumin and a few red blood cells. *Lumbar puncture* on the 12th day was clear and showed increased pressure, otherwise negative. On the 22d day pressure was markedly decreased, the fluid xanthochromic, with 10 cells. *Lumbar puncture* on the 60th day showed 20% block. Therapy, sedatives. *Course:* Levels of paralysis and sensation have not changed in 3 years; incontinence of urine and stools persist; no change in the reflexes.

TABLE 14.—THREE ADDITIONAL CASES OF ENCEPHALOMYELITIS FROM THE LITERATURE.

Author	Feldman and Bratalowsky.[13]	Gryzbrowsky [13]	Socin.[13]
Sex	M	F	F
Age	36	32	38
No. doses	3	3	2
Total dosage	0.75 gram	0.75 gram	1 gram.
Onset after last injection	1 day	1 day	2 days.
Chills	Yes	No	Yes.
Fever	Yes	Yes	Yes.
Salient neurologic signs and symptoms	Vomiting; convulsions; level lesion, atrophy; flaccid then spastic; sphincter disturbance	Unconscious; pupillary changes; level lesion; mening signs	Headaches; pupillary changes; mental disturb.; convul.; level lesion; sphincter disturbance.
Rash	Early	None	Early.
Treatment	Cal-chlorid; adrenalin; venesection; Hg and bismuth injection	Not stated	Not stated
Outcome	Level lesion persisted	Died in 6 days	Died in 14 mos.
Lues	Yes	Yes	Not stated.
Laboratory	Urine and spinal albumin	Urine and albumin	Spinal fluid cells incr.
Autopsy	....	Myelitis; encephalitis; pneumonia	No.

There is nothing characteristic in these 4 cases in regard to the clinical symptoms other than that they were a combination of

the encephalitic and myelitic pictures. A point of interest, though of questionable significance, is that 3 of the 4 cases had an exanthematous rash previous to onset of toxic symptoms. Also in 3 of these cases, the cerebral symptoms occurred before the spinal symptoms. One case came to autopsy and had a combination of brain and cord lesions.

Meningitis. Many of these cases, in addition to having brain and cord disturbances, gave clinical signs of meningeal involvement, such as rigidity of the neck, opisthotonos and a positive Kernig. The question of meningeal involvement in cases of hemorrhagic encephalitis has not been particularly emphasized.

In 146 cases of encephalitis, 93 came to autopsy. Of these, 24 showed evidence of meningitis. Clinically, 30 showed evidence of meningitis, of whom 3 recovered.

TABLE 15.—PATHOLOGY.

Autopsy.	No. of cases.
Brain examined	95
Cord examined	21
Complete autopsy	63
Total number autopsies	98

In the cases of encephalitis, 98 had autopsies and, of these, 3 autopsies did not include the brain and cord. In the 8 cases of myelitis, 4 had complete autopsies. In the 4 cases of encephalomyelitis, 1 had a complete autopsy.

According to Alpers,[129] the majority of cases shows the following characteristics: The gross lesions appear as pinpoint, bright red discolorations throughout the brain substance. These may coalesce to form large foci and are usually found in the white matter (centrum ovale, corpus collosum and internal capsule), but occasionally in the gray matter (basal regions and thalamus), and in the pons and basal ganglia. Hemorrhage, however, is not an essential part of the picture. Microscopically, in the center of the lesion capillary or pre-capillary vessels are observed, with swollen or destroyed endothelium. In some instances, the swelling is so great as to completely obliterate the lumen. Often the lumen contains a fibrin clot or a hyaline thrombus. Immediately next to the central vessel is an area of necrosis, completely surrounded by a palisade-like arrangement of intact glial cells. Beyond the collar of glial cells, which are many layers deep, there may or may not be an outer area of hemorrhage. The cells which surround the central necrotic area are oligodendroglial. There are some fibrous neuroglia cells immediately outside these areas. These foci may occur without hemorrhage. Alpers[129] states that hemorrhage is apparently of little importance, as in most instances hemorrhages were not seen in relation to these areas despite the fact that grossly the lesions appeared discolored. The presence of red blood cells in these areas

is usually explained by diapedesis. Alpers found that thrombi in the central vessels (capillary or pre-capillary) occurred infrequently, and that the endothelium of the central vessels was swollen or destroyed, and the vessel often occluded by the swollen endothelium. He explains the origin of these foci as follows: As a result of the injury to the endothelium by a toxin or infectious process, neuroglia cells are collected about the vessel. As the blood supply is cut off through the occlusion of the vessel by the *swollen* endothelium, or possibly by a thrombus, the central cells in the area become destroyed and, as the process extends, a larger area of coagulation necrosis develops. Some cases[17,63,76–80,89,98,110] showed at autopsy hyperemia and edema of the brain without any areas of softening or hemorrhage. Stuhmer[98] believes that edema of the brain always occurs first, and in severe cases is always followed by hemorrhage. The increased intracranial pressure, as shown in 25 of the 39 cases upon which lumbar punctures were performed, also tend to stress the presence of edema of the brain. According to Scott and Reinhart,[119] the cord reveals a diffuse myelomalacia involving both the gray and the white matter, marked edema, degenerative lesions of the bloodvessels with perivascular hemorrhages, and complete destruction of all ganglion cells of the anterior horn. There is no exudate or glial proliferation.

TABLE 16.—INVOLVEMENT OF OTHER ORGANS IN COMPLETE AUTOPSIES.

Organs.	No.	Percentage.
Lungs	27	42
Heart	15	23
Liver	11	17
Kidneys	24	38
Spleen	8	12
Stomach	3	5
Intestines	2	3
Thyroid	1	1.5
Aorta	1	1.5
Uterus	1	1.5
Pancreas	1	1.5
Skin	1	1.5
All organs	10	15
Larynx	1	1.5
Bladder and ureter	1	1.5

Examination of organs other than the central nervous system was carried out in 63 cases. Table 16 definitely reveals that pathologic changes existed in other organs, such as pinpoint hemorrhages, edema, cloudy swelling, fatty degeneration, congestion, all of these being caused by the arsphenamin reaction and being part of the generalized toxic reaction.

To date there have been numerous theories promulgated for the cause of arsphenamin central nervous system reactions, none of which particularly answers the problem.[23,38,61,62,89,98,101,126,133–168] They may be summarized as follows: (1) Action of the arsphenamin molecule itself, either by direct dilatation of the bloodvessels or by

indirect dilatation of the bloodvessels due to lack of adrenalin from destruction of the adrenal glands. The majority favors this theory. (2) Liberation of trivalent inorganic arsenic, due to faulty elimination of the drug due to kidney impairment. Ehrlich was the first to advance this theory. (3) Herxheimer reactions. May be ruled out in non-luetic cases. (4) Anaphylactoid reaction. (5) Allergic reaction. Schreiner[165] discusses the cutaneous disorders that develop in the course of arsphenamin therapy, such as the angioneurotic syndrome, the fixed arsphenamin exanthem, the generalized exanthem and the arsphenamin dermatitis. After calling attention to similarities between the cutaneous disorders resulting from arsphenamin therapy and the known allergic diseases, the author describes tests by which he attempts to prove the allergic character of the cutaneous disorders. In order to determine the presence of specific antibodies, he made cutaneous tests, and he was able to demonstrate the allergic nature of the symptoms in 18 of 20 patients presenting various forms of cutaneous disorders. (6) Uremia. Theory advanced by Stuhmer[98] and not mentioned by others. (7) Effects upon the reticulo-endothelial system.[137,145,151] Asuna and Kuhn[137] have shown a specific damage to the endothelial lining of the vessels. Hassko[145] believes that this damage is due to a defibrination of the blood. Experimentally he has shown that gelatin hinders these factors.

From the pathologic reports of the series of cases we have reviewed, it is apparent that there is a damage of the vessel walls. This is further substantiated by the work of Asuna and Kuhn,[137] Marschalko and Vezpremi[151] and Hassko.[145] Furthermore, similar changes have been found in cases that have died from organic arsenic poisoning; in addition, it must be remembered that this pathologic picture of so-called hemorrhagic encephalitis may be produced by the many other factors previously mentioned. It is apparent that the arsphenamin breaks down and eliminates free arsenic, as this was found in the organs in a number of these cases. Many explanations have been attempted to explain these facts, none being satisfactory, however. Why in certain people arsphenamin should be toxic and in others have no effect whatsoever is yet to be discovered. Furthermore, why the same patient, who has received arsphenamin 8 years (Bruhns and Löwenberg[12]) previously without developing any toxic reaction, then suddenly develops hemorrhagic encephalitis cannot be explained. Then, too, the same batch of drug has been used on a number of people, only 1 of the group developing symptoms. A case has been reported wherein the same ampule was divided between 2 patients (Miller[66]), injected at the same time; 1 of these developed a toxic encephalitis and the other did not. It is well known from reports of Newmark,[130] Vecki,[131] Fritz,[169] that this reaction may occur after intramuscular injection as well as intravenous injection. That it is not due to

syphilis is further emphasized by the 3 cases included in our reports, as well as the case of pneumonia treated by Henneberg.[38]

Prognosis. Of those with hemorrhagic encephalitis, 32 cases recovered; of those with myelitis, 1 recovered; and of those with encephalomyelitis, none recovered. Thus it appears that those patients with involvement of the spinal cord practically never recover, although they may live with a complete paraplegia after the symptoms have developed and die at a later time from a terminal infection. We have reviewed the encephalitis cases in hope of finding facts of prognostic value while the process is active. It is quite evident that the age, sex, total dosage of arsphenamin, number of doses of arsphenamin, time of onset of symptoms after the last dose and adjunct therapy did not in any way influence the progress of the disease.

It has been maintained by some authors, such as Scott and Moore,[95] Wechselmann,[105] that the adjunct therapy used in conjunction with arsphenamin was responsible for the toxic reactions. In our review, mercurial preparations, iodids and bismuth, etc., did not in any way increase the toxicity of arsphenamin. In approximately 47% of these cases, adjunct therapy was utilized, and in 53% arsphenamins were given alone.

Apparently the reaction cannot be traced to any particular fault of the drug or any particular faulty administration of the drug. The following observations indicate conditions that may be considered signs of grave prognosis: All of the cases with hemiplegia died. In 27 cases with meningeal signs and symptoms, only 3 recovered. The prognosis is unfavorable for the first 3 days, after development of signs and symptoms, 48% of the patients dying in this period. In this series of cases those that recovered from hemorrhagic encephalitis did so completely and had no residual symptoms. The therapeutic measures may be divided into prophylactic and curative.

Prophylactic Measures. (1) Arsphenamins should not be given to patients with damaged kidneys.[95,181] (2) The best care and technique should be used in administering the drug.[141,142,166] (3) Ephedrin sulphate (50 mg.) should be given for 2 days previous to injection[200]. (4) Adrenalin, 1 cc. of 1 to 1000 intramuscularly 10 minutes before injection. (5) Atropin sulphate, grs. $\frac{1}{150}$ hypodermically 15 minutes before the injection of arsphenamin.[201] Adrenalin, introduced by Milian, in 1912, has been used successfully by various writers.[25,149,162,170–180] It was Milian's belief that adrenalin insufficiency played a part in the causation of these symptoms. The vasodilator properties of these drugs in the presence of lessened adrenal activity lead to the production of these after effects, particularly upon the cerebral vessels. Rebaudi[182] recommended the use of amino-acids of the liver mixed with neoarsphenamin for patients who had an intolerance to the drug, especially as it permitted larger and more frequent doses of neoarsphenamin. He used

0.9 gm. of neoarsphenamin mixed with 2 cc. of amino-acid of the liver, stirring slowly with a glass rod until the color was yellow-gold.

Curative Measures. The curative measures may be given as follows: (1) *Against the toxic phenomenon:* (*a*) Adrenalin hydrochlorid, 1 cc. of 1 to 1000 intramuscularly followed by 1 cc. of 1 to 100,000 intravenously;[154,180] (*b*) sodium thiosulphate; (*c*) sodium dehydrocholate; (*d*) calcium thiosulphate; (*e*) calcium chlorid; (*f*) ephedrin sulphate; (*g*) 50% glucose solution. (2) *Sedatives:* Numerous sedatives have been utilized, such as chloroform, ether, morphin, codein, barbiturates, sodium amytal, Stroganoff therapy. (3) *Supportive measures:* Camphor and oil, intravenous saline, intravenous glucose (10%), digitalis, caffein, etc. (4) *Reduction of intracranial pressure:* Spinal or cisternal puncture, venesection, 50 cc. of 50% glucose in saline intravenously and decompression. No emphasis, however, has been placed upon the active dehydration measures. In 1920, Ravaut[177] called attention to the usefulness of sodium thiosulphate in a number of metallic poisons, such as arsenic, mercury, lead, bismuth, zinc and copper, as well as the sequelæ of arsphenamin. Busman and Woodburn,[183] McBride and Dennie[184] reported additional cases wherein it has been used. Stokes[170] advocates its use. This substance is one of a group of sulphur-containing salts and exerts a favorable influence by reduction of the metallic poisons to their non-toxic sulphids, and thus stops the toxic action and aids elimination. Marples and Myers[185] believe that the effect of sodium thiosulphate in these cases is due to the stimulation of that mechanism which normally takes care of the elimination of arsphenamin. They believe that the release of heavy metals from protein combination following sodium thiosulphate administration is rapid, and that they are liberated by the formation of heavy metal salts of thiosulphuric acid. Calcium thiosulphate has been used for postarsenobenzol complications.[186] The dose recommended is 5 cc. of a 10% solution daily for 3 days, and subsequently 2 and 3 times a week. Calcium chlorid has been used for the prevention of certain cutaneous inflammations by Chiari and Januschke,[187] in 1911, Blum,[188] in 1921. On theoretical grounds the combination of calcium and thiosulphate should be advantageous, particularly in those groups where sodium thiosulphate has failed. Solomon[189] found calcium chlorid was useful in the prevention of nitritoid reactions. Stokes[200] thinks that the detoxifying and irritation-reducing effect of calcium can be accomplished by using 10 cc. of calcium gluconate intravenously or intramuscularly just before the arsphenamin injection. This has seemed to smooth the course of some otherwise exceedingly reactive patients. Lipskeroff and Grebin, following the methods of Oliver, Yamada and Kulos,[191] tried blood serum and water diluent for neoarsphenamin, and found that it did not reduce toxicity. The use of water with calcium chlorid added[192,193] was found less toxic. This was corroborated by Lewin by using glucose solution as suggested by

Weitgassen,[194] and a marked reduction of toxicity was found. This reduction of toxicity by the use of glucose solution has been noted by numerous other authors.

In the 5 cases of myelitis, no attempts have been made to carry out the Queckenstedt test, as at the time of these case reports this newer method of diagnosis was unknown. In the case of encephalomyelitis under our observation the Queckenstedt test revealed a definite block. Furthermore, xanthochromic fluid was present, further verifying the presence of block. The rationale of laminectomy in such cases is borne out by the experimental work of Allen,[195] who indicated that in dogs a cord edema following trauma reached its maximum pressure within 4 hours. McVeigh[196] believed that the cord edema reached its maximum within 8 hours. It was the belief of Allen that this swelling of the cord, secondary to edema caused the nerve damage, and for this reason he recommended early laminectomy with longitudinal slitting of the cord. In these cases the edema occurs before the hemorrhagic process develops and such therapy is definitely indicated. Coleman,[197] in cases of spinal cord trauma, has advised the use of the Queckenstedt test to determine the presence of spinal block. This test is carried out by performing a spinal puncture and compressing the jugular vein. The rapidity of the rise and fall of the spinal fluid in a water manometer indicates the presence or absence of block (Stookey and Klenke[198]). Naffziger[199] believes that the traumatic cases should be placed in the category of an early emergency operation, and agrees with Coleman in advising early laminectomy, particularly when the fluid does not rise at all in the spinal manometer by jugular compression. In view of the serious outcome of these cases, it is our opinion that the Queckenstedt test should be performed daily to determine whether a block is present and, should any evidence of block occur, we advise a decompressive laminectomy at the level of the lesion. It is our belief that dehydration measures are actively indicated in these cases, and that the acute brain and cord edema that arises plays an active part in the final outcome of the case. An acute brain edema with rise of intracranial pressure is part of this picture and has been previously called to our attention by Ehrlich,[23] Hammer,[36] and also by Stuhmer[98] who in the early days recognized its importance and advised decompression. Eight cases that came to autopsy showed brain edema and hyperemia without hemorrhage. Furthermore, in the 39 cases that had lumbar puncture, 25 showed evidence of increased intracranial pressure. For dehydration measures, we advise the use of 50 to 100 cc. of 50% glucose solution intravenously every 3 to 4 hours; retention enemas consisting of 6 ounces of magnesium sulphate crystals dissolved in 4 ounces of water. Should the pulse become too rapid glucose may be given in less frequent amounts, and normal salt be given intravenously. If these measures prove of no avail, lumbar puncture may be performed repeatedly with the removal of 25 to

50 cc. of fluid. Judgment must be exerted during the course of the disease as to the limitation of fluid intake. In some cases this is advisable, in other cases undesirable. If brain edema continues to increase with its resulting rise of intracranial pressure, subtemporal decompression with drainage of the subarachnoid space should immediately be carried out. Subtemporal decompression has been performed in 3 patients.[2,12,98] In 1 the brain appeared normal, and in 2 the brain and meninges were edematous. All of these patients, however, succumbed to the procedure.

Conclusions. 1. The mortality of cases with central nervous system involvement secondary to intravenous injection of arsphenamin is about 76%.

2. There is approximately 1 death due to central nervous system involvement in every 5398 cases treated, and in every 28,768 injections.

3. The term, "hemorrhagic encephalitis," is not adequately descriptive.

4. The toxic reaction may occur in non-luetic cases, is not related to the quantity of the drug given, nor the number of injections, nor the toxicity of the drug itself. It is not related to the age of the patient nor the sex. It occurs most frequently after the 2d dose, though it has been reported as occurring after the 15th dose. Furthermore, cases have been reported where the drug has not at first produced toxic effects, but when again given several years later toxic reactions resulted. The symptoms may occur from 12 hours to 70 days after the injection, but usually develop from 12 to 144 hours.

5. The outstanding symptoms are headache, vomiting, nervousness, chills and dizziness, with physical signs of fever, cyanosis, respiratory and pulse changes. The outstanding neurologic signs are convulsions, unconsciousness, pupillary and ocular muscle changes, reflex changes, loss of sphincter control, mental disturbances, hemiparesis and rigidity of the neck. Laboratory reports indicate the presence of an acute nephritis in a relatively large percentage of the cases as well as an increased spinal fluid pressure.

6. Myelitis and encephalomyelitis may also occur, while meningitis may coëxist.

7. This toxic reaction is diffuse rather than focal, as pathologic reports and clinical findings indicate involvement of the other organs. The clinical diagnosis is derived from the organ indicating the greatest involvement, *e. g.*, if the brain shows predominating clinical signs, it is an encephalitis; if it is the cord, it is myelitis; if the liver, a hepatitis.

8. The methods of therapy have been described in detail and consist primarily of prophylactic and curative measures. The curative measures are detoxification and reduction of intracranial pressure by medical or surgical methods. Sedatives and supportive measures should be utilized.

SPONTANEOUS RUPTURE OF THE ESOPHAGUS IN SYPHILIS.

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Many physicians believe that the esophagus is relatively immune to pathologic processes, and that, barring congenital defects, trauma, cardiospasm, constrictions, varices, benign and malignant neoplasms, it may be disregarded as a seat of disease. Mosher,[1,2,3] however, in the largest reported series of postmortem specimens studied has conclusively shown that the esophagus is much more vulnerable to every type of lesion than has heretofore been the popular belief. In one series of 100 consecutive organs obtained from routine autopsies he found pathologic lesions in 14 specimens. These were septic emboli, acute and chronic inflammations, degenerations, benign tumors and the like. His studies emphasize the need for a more careful study of this organ in the routine autopsy.

Spontaneous, non-traumatic, complete rupture of the esophagus is a rare condition, if the number of reported cases in the literature is any criterion. Gott[4] as a result of such a survey on the subject discovered only 38 such cases, the first being the celebrated one of the Baron Wassenau in 1724. Gott added 4 cases, 2 of which were due to multiple bacterial emboli occluding the esophageal capillaries in patients with meningococcic meningitis. He concluded that cardiospasm, stricture, ulcerations, esophagitis and vascular changes in the esophageal wall predispose to rupture.

Mallory and Weiss[5] observed 15 patients who, after long alcoholic debauches, developed massive hematemesis. They reported the postmortem findings in 4, all of whom showed lacerated but not ruptured lesions of the cardia of the esophagus. As none showed any evidence of liver cirrhosis it was concluded that the hematemesis was not from ruptured varices due to liver cirrhosis. They suggested that the lacerations may have been produced by pressure changes in the stomach during retching, vomiting and regurgitation. They felt that such lesions could develop in other conditions in which severe retching and vomiting occurred, such as in pernicious vomiting of pregnancy and neoplasms. In a later report[6] these authors presented 2 more instances of lacerated esophagi in patients —also alcoholics—both of whom died and the autopsies revealed lacerations through the esophageal mucosa. Gott agreed with them

that the inciting cause of either laceration or rupture of the esophagus was sudden, increased, intra-esophageal pressure.

There has not been found any reported cases of rupture of the esophagus due to luetic periarteritis of the esophageal wall. Luetic periarteritis leads to ischemia of the part supplied by the artery with subsequent arterial occlusion by scar formation. This scarring materially weakens the wall the extent of which is dependent upon the size of the scar. If the scar includes a portion of the lining mucosa, the autolytic enzymes from regurgitated gastric contents would have a vulnerable point of attack which could more easily erode the wall. Such a sequence of events would be a combination of etiological factors expressed by Mosher, Gott and Mallory and Weiss as tending to enhance the possibility of laceration or rupture.

In syphilitic patients, any organ or combination of organs including the esophagus may be affected by the disease. Then, too, in those patients with central nervous system involvement, retching and vomiting occasionally occur. The combination of esophageal periarteritis and severe retching and vomiting (during "paretic seizures") should offer rather good possibilities of either lacerations or ruptures of the esophagus. In spite of this, apparently the incidence of such occurrence in the literature is *nil*. It is our feeling, however, that this may be due, in part at least, to the fact that the esophagus is generally disregarded in the routine postmortem examination. In our own institution, in the last 436 consecutive autopsies performed, 44 were on patients with syphilitic central nervous system involvement. Of these, only 5 died during "paretic seizures." Of these latter, 2 patients died of hemorrhage resulting from complete, non-traumatic rupture of the esophageal wall. In no instance were lacerations without complete rupture found. The following case record abstracts are from the records of these 2 patients.

Case Abstracts. Case 1.—A. R. (No. 38909), a white girl, aged 12, a congenital luetic diagnosed as having juvenile paresis, was admitted to the Worcester State Hospital in 1929 having received specific treatment for several years before admission. Her subsequent study revealed a rather typical clinical and laboratory picture of juvenile paresis for which she received malaria, bismuth and sulpharsphenamins. She eventually had repeated paretic seizures which lapsed into status epilepticus. On the 3d day prior to death (1932, age 15) she had a maximum number of daily seizures which reached 50. The rectal temperature rose rapidly to 106, pulse fluctuated between 130 and 140 and respirations from 30 to 50. Her pupils were unequal and irregular and reacted sluggishly to light. There were impaired resonance and increased breath sounds and râles at both bases. The blood pressure was 90/70. All of the peripheral nerve reflexes reacted sluggishly to stimulation. No patellar reflexes were elicited. Babinski reflexes were obtained on both sides. She was semicomatose for 3 days and died suddenly.

Autopsy. (2.3 hours after death.) No evidence of postmortem degeneration. The patient was found to have died of complete rupture of the esophagus. The posterior mediastinal space contained approximately 100 cc. of a thin, "coffee-ground," black colored material, undoubtedly

gastric and esophageal contents. In the left lateral wall of the esophagus was a longitudinal rent measuring 3.1 cm. long, the caudal end of which was 2.3 cm. above the cardia. The esophageal wall surrounding the rent was completely hemorrhagic and black. The edges of the rent showed, in addition to the massive hemorrhage, many esophageal vessels with a perivascular infiltration of lymphocytes, endothelial leukocytes, some plasma cells and fibroblasts. Complicating the picture were numerous pigment laden leukocytes and edema. Rare spirochetes were found by special staining methods.* The other viscera were essentially normal.

FIG. 1.—Case 1. Esophagus showing longitudinal rent and hemorrhagic mucosa. The rectangle of tissue removed below the rent was taken for microscopic examination. Note the thinness of the wall and the absence of normal rugæ.

CASE 2.—C. E. (No. 36285), a white male, aged 49, was admitted to the Worcester State Hospital in 1925 with a diagnosis of "psychosis with cerebrospinal syphilis." His syphilitic condition had been treated with tryparsamid and bismuth. In 1930 he developed signs and symptoms of duodenal ulcer without complete obstruction, confirmed by laboratory and Roentgen ray findings. For the last 1½ years he had had paretic seizures. On July 10, 1932, he rapidly became jaundiced, the abdomen became distended and the liver edge was felt 2 cm. below the costal margin. Ascites developed with shifting abdominal dullness. His icterus intensified. He began to vomit and have hiccoughs. On July 15, he had occult blood present in vomitus for the first time, gradually became comatose and expired (5 days after the onset of jaundice). His temperature, pulse and respirations remained normal to the end.

AUTOPSY. (2 hours after death.) Showed that the patient died of complete rupture of the esophagus with hemorrhage. Figures 2 and 3 give an idea of the extensive hemorrhage in the wall of the ulcer itself. The rent was 3 cm. in length, the caudal end of which was 1.5 cm. above the esophageal gastric junction. The posterior mediastinal space contained about 75 cc. of a thick, mucoid, "coffee-ground" colored fluid. In the histological study of this specimen the hemorrhage was so extensive as to almost obliterate the histological architecture of the wall surrounding the rupture. In

* The type of stain used for spirochetes is a modified silver stain after De Galantha (Am. J. Clin. Path., **2**, 63, 1932).

addition, this patient had an atrophic cirrhosis of the liver (weight 940 gm.), almost simulating a "classical Hepar Lobatum," with ascites and jaundice. The remaining viscera showed lesions consistent with his age and relatively irrelevant.

FIG. 2.—Case 2. The unopened esophagus showing the complete rupture near the cardiac orifices. A white glass rod is in the lumen of the esophagus. Note the markedly hemorrhagic wall.

Discussion. In the first case, it is demonstrated that syphilis caused the periarteritis in the esophageal wall. It is logical to assume that these lesions materially weakened the wall. Attacks

FIG. 3.—Case 2. Same specimen as in Fig. 2 after opening. Note the markedly hemorrhagic mucosa and complete absence of the normal rugæ. Note the large crater-like area surrounding the hole of the rupture. In this specimen, only the proximal 2.3 cm. of the esophageal wall was normal.

of retching such as are present in paretic seizures cause extremes of intra-abdominal pressure which are easily transmitted through the diaphragm to the wall of the esophagus. The regurgitation of autolytic gastric contents over the lining of the esophagus which

has been already damaged by the luetic reaction tends to erode it, allowing these contents to come in contact with the muscular layers.

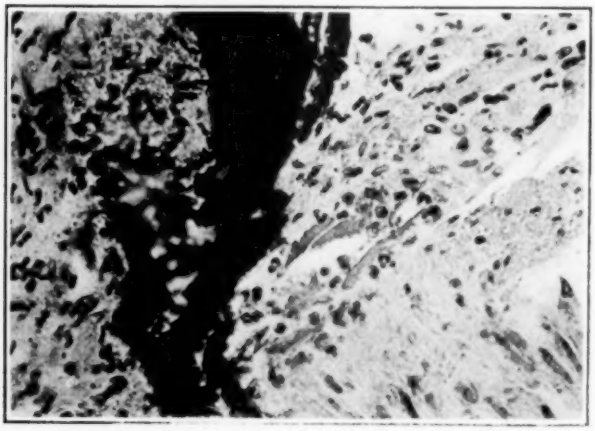

FIG. 4.—Case 1. Microphotograph of luetic perivascular infiltration of lymphocytes and endothelials, with occlusion and scar formation in the wall of the esophagus, near the area of eruption. Note large hemorrhagic areas in the scarred wall. Magnified 400 ×. (Due to the large amount of blood pigment the spirochetes photographed too poorly for reproduction.)

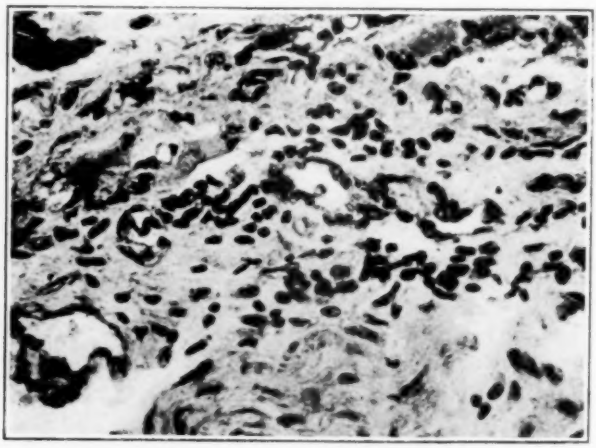

FIG. 5.—Case 1. Microphotograph of section of the esophageal wall, showing hyperplasia of the endothelials with perivascular infiltration of fibroblasts and lymphocytes, with partial occlusion of one vessel. Magnified 400 ×.

To substantiate this hypothesis, the epithelial lining around the rent in both specimens was almost completely denuded. We have, therefore, in both instances a weakened esophageal wall being

acted upon by autolytic enzymes and severe intra-abdominal pressure, forming an ideal point of rupture.

In 496 consecutive autopsies performed on mentally ill patients, 5 were found to have died during a paretic seizure and of these latter, 2 (40%) died of a sudden complete rupture of the esophagus. Although the actual number of those dying in paretic seizures is small and percentages drawn from such a small sample are wholly inadequate, yet the relatively large number (40%) of those dying of rupture of the esophagus shows the tendency of such occurring more frequently than the literature would lead one to suppose.

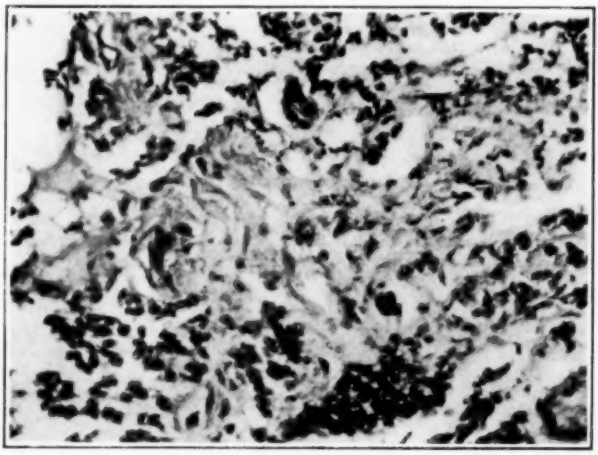

FIG. 6.—Case 2. Perivascular infiltration and occlusion deep in the wall of the esophagus. Note the large scarred area in the center of the picture. Magnified 400 ×.

Summary. Syphilitic periarteritis of the esophageal wall usually leads to vascular occlusions, scar formation and damage to the epithelial lining at those points. Luetic patients in whom the central nervous system has been involved in the disease process may have attacks of the so-called "paretic seizures" of which retching and vomiting are prominent features. The combination of the esophageal scars, sudden extremes of intra-abdominal pressure and the autolytic action of the regurgitated enzymes of the gastric contents may result, in rare instances, in sudden rupture of the esophageal wall.

Two case reports are presented, both on patients who died from sudden, complete rupture of the esophageal wall. One was a 15-year-old congenital luetic with the juvenile form of general paresis. The second case was that of a 58-year-old patient suffering from acquired lues with central nervous system involvement. Each died during an attack of "paretic seizures."

Conclusions. Complete rupture of the esophageal wall may occur, in relatively rare instances, due to syphilitic periarteritis of the organ and severe retching and vomiting which is a rather common accompaniment of paretic seizures.

A routine, detailed examination of this organ in all autopsies is urged.

The esophagus is more vulnerable to pathologic lesions than the statistics have heretofore indicated.

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OBESITY TREATMENT BY DIET, THYROID AND DINITROPHENOL.

Result on 106 Outpatients.*

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Since 1930, patients complaining of obesity have been referred to the Endocrine Clinic for systematic treatment. Diet and thyroid carefully dosed have been our mainstays, and some other glandular extracts have been tried. While an analysis of the material was in progress, Prof. Tainter suggested, in the fall of 1932, that dinitrophenol might be useful in the treatment of obesity, and with his associates has published exhaustive metabolic studies of its pharmacologic effects in both animals and man, including the obese. The drug was, therefore, added to the methods which were already being surveyed under the far from ideal but fairly uniform conditions of outpatient care.

Material. The records of some 200 obese patients who attended the Endocrine Clinic during the period between January, 1931, and May, 1933, were sifted. Growing children were excluded, so that all patients were

* Aided by the Rockefeller Fluid Research Fund.

adults, except for 3 girls between 16 and 17 years whose records showed no growth at time of treatment. Complicating disease was taken as cause for exclusion only where it seemed likely to induce weight changes, as, for instance, heart failure with edema or uncontrolled diabetes mellitus.

Concerning attendance and coöperation, no very rigid standard was set up. All those included had attended clinic at least 3 times, with an interval of at least 30 days between the first and last visits. They had kept their appointments with fair regularity, and made a reasonable attempt to follow advice. In some patients coöperation varied, being good in some periods and obviously bad in others, so that the latter periods were discarded. The main difficulty in securing coöperation, of course, was in regard to diet; there was never an objection to taking oral medicine. No records were disqualified because the weight loss was disappointing.

The residuum consists of records of 104 women and 2 men. All were white except 2 women.

Therapeutic Procedure. Patients came to this special clinic only after a history had been taken and a physical examination done in the medical clinic. Laboratory work included urinalysis and basal metabolism on all patients, and blood sugar or sugar tolerance tests and Roentgen rays of the sella where indicated. The net height was determined at the first visit, and records of net weight (by subtraction of 3 to 5 pounds for women's clothing and 6 to 8 pounds for men's, as seemed appropriate) made at every visit.

At the first visit each patient was given a copy of a reducing diet, containing 80 gm. of carbohydrate, 60 gm. of protein and 40 gm. of fat, giving a total of 920 calories, outlined in grams and household measures, to show the exact food distribution recommended for 3 meals a day. It had provision for vitamins and salts. The patient was asked to approach the prescription as closely as possible, and to bring an estimate in ounces or tablespoonfuls of the food eaten the day before attendance; this actual list was then calculated at each visit.

Patients were kept on this simple dietary régime so long as the loss was satisfactory, *i. e.*, at least 2 pounds per month, continued moderate loss being preferred to more dramatic reductions. Many patients reached their ideal weight by dieting only. In general, drugs were added when the patient's weight had been stationary for 2 visits. They were tried in turn and singly, each new régime being maintained so long as it was effective or until it was shown to be ineffective. Continuance of diet was insisted on. No effort was made to control the water metabolism in this series.

In making the analysis, each type of treatment, *i. e.*, diet alone, diet plus thyroid and diet plus dinitrophenol, was considered as a separate period. The various preparations other than thyroid and dinitrophenol used during the study are not presented here.

Diet Alone. One hundred patients were on a period of dietary régime before medication; 72 of the 100 became stationary in less than 4 months; the remaining 28 were on diet for periods of 4 months to 1 year or more.

Diet Plus Thyroid. This group included 51 patients. The dose was 1 grain daily of desiccated thyroid (Armour) for a week, then gradual increase to tolerance. This was measured, not by basal rates (too expensive), but by too rapid pulse, nervousness, headache or other discomfort. The pulse as taken at the clinic was not allowed to go above 100. The maximum daily dose usually turned out to be 2 or 3 grains, and the average dose was 1½ grains.

Of the 51 patients, 41 were given thyroid after they were stationary on diet alone, 6 simultaneously with diet (on account of symptoms of hypothyroidism) and 4 after dinitrophenol.

Diet Plus Dinitrophenol. This group included 23 patients. The drug was given and dosage controlled just as for thyroid, according to clinical indications and not by basal metabolic rates. The drug was put up in 75-mg. capsules or, more recently, in equivalent 100-mg. capsules of sodium dinitrophenol. Patients were first tried on 1 capsule daily for 1 week before the dose was gradually brought up to tolerance. The maximum daily dose in this series was 300 mg., and the average daily dose was 165 mg. It was taken all in 1 dose, with at least 250 cc. of water to follow, thus avoiding any epigastric discomfort after swallowing; and usually in the evening, so that the flushing and heat which occur particularly a few hours after administration should come on in bed. No more than a week's supply was given, and every patient was sharply warned against taking any more than the daily ration prescribed.

Analysis of Data. For every type of treatment the *means* were calculated for the following: age, basal metabolic rate and weight at beginning of treatment; daily caloric intake and dosage during treatment; length of period and weight loss before treatment; and number of days and weight loss on treatment.

The *time factor* in treatment proved a difficult one to evaluate because the length of time between visits and consequently the lag in the manipulation of treatment depended much more on the convenience of the patient than on the demands of good practice. Consequently, the total average weight loss on any particular régime which was maintained so long as it was effective, seemed a better measure of effectiveness than a rate of loss. Nevertheless, the durations of treatment were calculated, and where they seem to be significant will be mentioned. In a future analysis, when more evidence is at hand, the study of the rate of loss in pounds per day is expected to be profitable.

Periods longer than 1 year represent largely the records of patients who had been on a self-imposed effective home diet before enrolling in the clinic, and whose records were extended backward retroactively to include their preliminary efforts. Their records are in every case pooled with the 1-year periods.

Results. *Diet alone* took off approximately 15 pounds in about 3½ months, and thereafter not much more (until medication was

added). About 1 in 4 patients, however, lost as much as 20 pounds in this time, achieving finally about 30 pounds' total loss, with an occasional patient losing as much as 60 pounds. It was often not clear why some patients succeeded so much better than others, but in general weight loss was related to original weight, basal metabolism and duration of treatment. Specifically, weight loss and original weight showed a slight positive correlation ($r = 0.33 \pm 0.06$), *i. e.*, the heaviest patients tended to lose the most. Also, when the basal metabolism was normal the patients lost better than when it was depressed ($r = 0.24 \pm 0.07$). The time on treatment is likewise related, although it is too variable a factor to warrant converting the figures into rates of loss.

Patients' reports of diet were apparently inaccurate. Although reports varied between 400 and 1600 calories, the weight loss varied with the reported caloric intake only in that the loss was less where the diet was admittedly above 1200 calories. Age also appeared to be a negligible factor in the present study.

Based on the above considerations, thyroid and dinitrophenol may now be discussed.

Diet Plus Thyroid or Dinitrophenol. When patients had become stationary on diet alone, roughly after 10 to 20 pounds had been lost, it was possible to induce a further loss of about 12 pounds with either thyroid or dinitrophenol. Specifically, this further loss averaged 11 pounds for 41 patients on thyroid *versus* 12 pounds for 13 patients on dinitrophenol. When the basal rate was low, both drugs appeared to be more effective than when it was normal, but the number of patients was too small to prove this. Where the basal metabolism was normal (above -5%), the dinitrophenol appeared to be more effective than the thyroid: in pounds' loss, 12.67 ± 1.47 (average of 9 patients) against 7.38 ± 1.58 (average of 16 patients). This dinitrophenol loss was accomplished in 51 days and the thyroid loss in 93.

It must be emphasized that, even here, where the weight loss is almost twice as great on one treatment as on the other, the figures do *not* prove to be statistically significant on account of the limited numbers and wide distribution of results. This is true of all the figures reported in this paper (and, in fact, in many clinical papers).

Nevertheless, the results of the study do show consistent tendencies which appear to be worth presenting, and which deserve to be extended into studies on larger series.

Thyroid Dinitrophenol Switch and Vice Versa. After patients had become stationary on diet alone followed by the addition of either thyroid or dinitrophenol, *i. e.*, after about 20 pounds were lost, another 4 pounds' loss was forced by switching from thyroid to dinitrophenol (average of 6 patients), and also 4 pounds (average of 4 patients) by switching from dinitrophenol to thyroid. Since neither drug was notably effective in second place, this may mean

that, although on dinitrophenol patients apparently lose faster, they do not, on the average, lose more. This is a point which we particularly wish to investigate further.

Three groups which do not fit into the above classification are considered next.

Thyroid Instituted Immediately. Six cases in which thyroid was given immediately, along with diet, lost an average of 22 pounds, which is essentially the same as the loss shown by those patients who were given diet first and thyroid later. The time of treatment was around 7 months in both instances. This fact permits the conclusion that there is no advantage in starting medication until diet alone has accomplished all it can.

Dinitrophenol Without Diet. Separately considered are the 3 patients who failed to restrict their diets while on dinitrophenol. Their loss was *nil* (gained 1 pound, gained 8 pounds and lost 9 pounds respectively) during an average period of 62 days and on an average daily dosage of 200 mg. These 3 patients are of more interest than the usual cases of overeating because they had always been uncoöperative and were chosen for just that reason in order to see whether weight loss could be forced, even on an unrestricted diet. No final conclusions are justified from 3 cases, but it would seem probable that, at least on moderate dosage of dinitrophenol, no weight loss is to be expected unless the patient is likewise restricting his caloric intake.

Side Effects of Dinitrophenol. Ill effects were noticed in 3 cases: 1 patient reported nausea after the first few doses and did not continue with it; another finally stopped because she complained that she was "burning up;" a third patient was getting good results but was taken off the medicine after 7 days because she appeared somewhat jaundiced, a phenomenon which is now known to be due, not to liver damage, but to the coloring of the serum by the dinitrophenol itself. Other patients were able to continue with no unfavorable symptoms except flushing, occasional nightsweats and subjective feeling of heat.

Summary. The methods used in treating 106 unselected obese patients in the outpatient clinic were analyzed, with reference to the effects of diet alone (100 cases), thyroid (51) and dinitrophenol (23).

The weight losses shown here are not so great with any of these methods as could have been achieved if patients had restricted their diets more conscientiously. They do, however, represent the sort of results which may be expected in outpatient care of unselected patients, and, therefore, permit the following tentative practical conclusions:

1. Diet alone will take off an average of 15 pounds in $3\frac{1}{2}$ months and, therefore, should be the first therapeutic procedure in the treatment of obesity.

2. When dieting fails to get results, either thyroid or dinitrophenol appears to be an effective adjunct.

3. As an adjunct to diet, dinitrophenol is at least as effective as thyroid and, in patients with normal basal metabolism, possibly superior.

4. Thyroid given immediately with the beginning of diet caused no better weight loss than when it was given only after loss on diet had stopped.

5. Dietary control was necessary to achieving results with dinitrophenol, as it was to getting results with thyroid. Furthermore, reasoning from the thyroid results by analogy, it would seem that it is worth while removing as many pounds as possible on diet alone before exhibiting the dinitrophenol—this on the assumption that with any drug which is not compensating a physiological deficiency, the less given, the better for the ultimate health of the patient.

6. It should be emphasized that neither thyroid nor dinitrophenol should be used indiscriminately by patients unguided or under the direction of physicians inexperienced with their use.

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A PRELIMINARY REPORT ON THE CLINICAL APPLICATION OF A POLYVALENT STAPHYLOCOCCUS BACTERIOPHAGE IN BRONCHOSCOPY.

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and

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Eight years ago we attempted similar experiments in this clinic. At that time an autogenous polyvalent phage was developed by Dr. G. R. Moffitt. The attempt to make this practically available was abandoned for three reasons, namely: (1) the expense attached to its development in each individual case; (2) the elapsed time before the phage was available for injection; (3) the product proved extremely unstable.

A commercial bacteriophage, with a mercurial salt preservative, was used for a 3-month period in this clinic. The results of this therapeutic agent have been variable. On the basis of such varia-

bility this commercial bacteriophage was tested for its living and active properties. It was contacted against several stock strains of staphylococcus with a yeast extract broth (Savita) as a medium.[1] A "Cross-test" was performed with the above stock strains and the commercial bacteriophage by plating the young sensitive stock strains on a yeast extract and 1% agar plate and then touching this inoculation with a small needle loop full of bacteriophage. The commercial bacteriophage did not show lysis or produce a "clearing" with the stock strains of bacteria. With these two negative tests, and on the basis of Rakieten's work it was assumed that the bacteriophage had been destroyed by the mercurial salt present in the preparation. The phage used had about one-half the quantity of mercurial salt as that supplied to the profession.

An active polyvalent bacteriophage for staphylococci and streptococci has been prepared and is now used in the clinic. Several stock strains of staphylococci and streptococci were contacted to three polyvalent staphylococcus and streptococcus strains of bacteriophage.[3] Young sensitive stock strains of the above bacteria (18 to 24 hours), in a Savita-broth medium, were contacted to the stock bacteriophage. This bacteriophage-bacteria mixture was incubated for 24 hours at 37° C. and examined for lysis. Lysis was found to be complete and the control tubes checked this reading. In conjunction a "Cross-test" was made, using the same strains of bacteria and bacteriophage; all bacteriophage strains were found active on reading the agar-Savita plate after 24 hours of incubation at 37° C.

The tubes of bacteriophage-bacteria showing lysis after 24 hours were filtered through Chamberland filters (L_5). The filters were prepared prior to each filtration by subjecting them to muffled heat up to a red glow, cooling, packing and autoclaving for 30 minutes at 15 pounds pressure. A specimen of this bacteriophage filtrate was plated on Savita agar and tested for sterility. The filtrate was ampuled in 5 cc. sterile vials, closed by flame, and put in an incubator at 56° C. for 1 hour, for 3 different times. A final turbidity "Tyndall Effect" reading was made on the filled ampules; some of the filtrate also remained at room temperature, approximately 20° C., for several days and was read for turbidity.

Twenty-eight patients were treated, including 14 with bronchiectasis, 10 with lung abscess and 3 with chronic bronchitis. Of 10 in whom the commercial bacteriophage was used, 4 showed improvement; 6 showed no improvement, either clinically or symptomatically, and 1 died of an intercurrent pulmonary hemorrhage. Eighteen patients were treated with the special bacteriophage prepared for this clinic. All but one showed decided improvement after 2 or more instillations. Two were discharged from the clinic apparently cured.

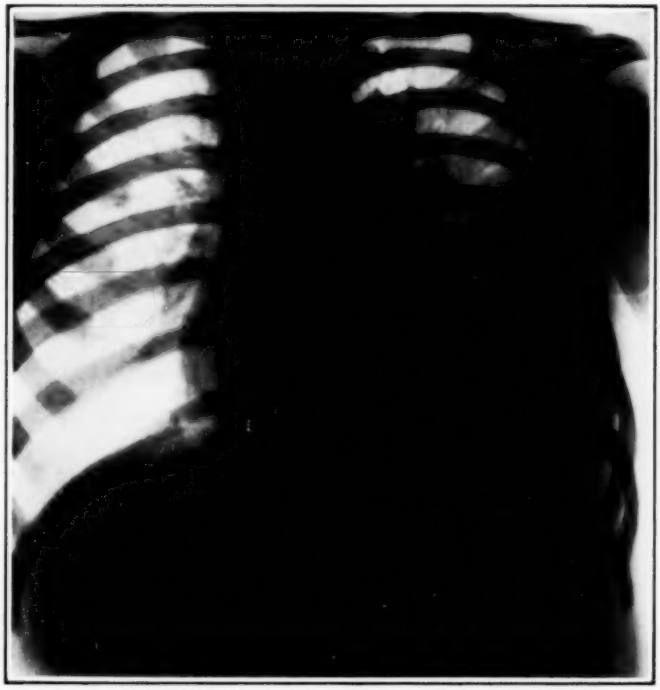

FIG. 1.—Case 15, Table 2, lung abscess, bronchiectasis, both lobes left side.

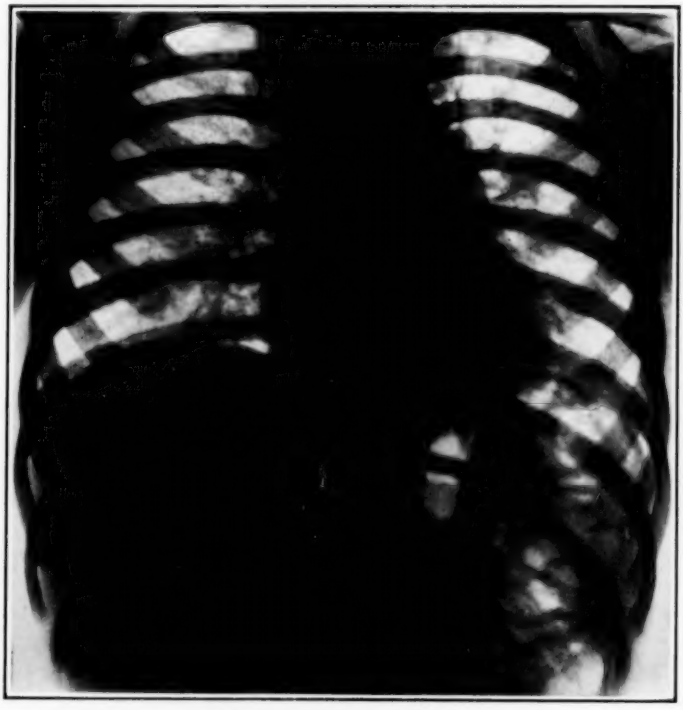

FIG. 2.—Case 15, Table 2, after two instillations of bacteriophage.

TABLE 1.—RESULTS IN 10 PATIENTS TREATED WITH A COMMERCIAL BACTERIOPHAGE.*

Cases.	Diagnosis.	Laboratory findings.	No. of treatments.	Improved.	Unimproved.
1. J. S.	Bronchiectasis	Strep. viridans; pneumococcus	3	+	
2. J. T.	Bronchiectasis	Strep. viridans; pneumococcus	3		+
3. F. A.	Bronchiectasis and lung abscess	Pneumococcus, strep., M. catarrh., and H. influenzæ	1		+
4. R. B.	Bronchiectasis	Pf. bac., pneu., strep., M. catarrh., non-hem. strep., diphtheroids	2		+
5. I. B.	Bronchiectasis	No specimen	5	+	
6. P. H.	Bronchiectasis	Strep. viridans, staph. albus	1	+	
7. J. R.	Bronchiectasis	Pneumococcus, hemolytic staph. albus	5	+	
8. O. S.	Bronchiectasis	No specimen	2	(Died pul. hem.)	+
9. K. A.	Empyema	Overgrown with B. subtilis	1		+
10. M. B.	Lung abscess, extensive involvement	No specimen	1		(Died) +

* Commercial bacteriophage with the addition of a mercurial salt.

Technique. Patients were treated at 7-day intervals, except during a 2-week period, when the phage was not available. All cases of pulmonary suppuration were treated, with the exception of those with a bronchoscopically evident bronchial asthma considered to be of extrinsic origin. The technique was the same as that used in the bronchoscopic treatment of any pulmonary suppuration. The draining bronchus or bronchi were localized; any impediment to free drainage was removed either at once or gradually and the secretion present thoroughly aspirated. A specimen was taken directly from the bronchus in a special collection tube for laboratory examination and culture, insuring against contamination by buccal or throat secretions. Five cubic centimeters of the bacteriophage were then injected directly into the bronchus, previously cleared by aspiration. An attempt was made to have this retained by instructing the patient to check the cough as long as possible.

Observation. Adequate and continued drainage is the bronchoscopist's chief aim in dealing with pulmonary suppuration. Thick, viscid secretions undoubtedly impede ciliary action[4] and may partially or completely obstruct a draining bronchus. It was therefore noteworthy at subsequent bronchoscopies after the use of our bacteriophage that the secretion was both less in quantity and altered in quality, the secretion becoming much thinner and the

odor markedly less. One patient with illness of 4 years' duration received regular bronchoscopic treatments for the last 2 years, including also injections of the commercial stock phage, without much benefit. In the past 3 months, since receiving our special bacteriophage, she has progressed remarkably, with improvement, as evidenced by lessened productive cough, after the first instillation.

TABLE 2.—RESULTS IN 18 PATIENTS TREATED WITH A SPECIAL POLYVALENT STAPHYLOCOCCUS BACTERIOPHAGE DEVELOPED AT THE PHILADELPHIA GENERAL HOSPITAL.

Cases.	Diagnosis.	Laboratory findings.	No. of treatments.	Improved.	Unimproved.
1. W. Mc.	Lung abscess	Overgrown with B. proteus	2	+	
2. J. K.	Lung abscess	Strep. viridans, Staph. albus	4		(Died) +
3. T. R.	Lung abscess	Pneumococcus	12	+	
4. J. RO.	Lung abscess	Myriads of hemolytic strep. and B. influenzæ	4	+	
5. E. W.	Lung abscess	Strep. viridans, pneumococcus	4	+	
6. W. L.	Chr. bronchitis	No specimen	3	+	
7. M. M.	Chr. bronchitis (rt.)	Strep. viridans, Staph. albus	4	+	
8. M. L.	Pulm. suppuration (rt.)	Gauze packing: no growth	4	+	
9. W. H.	Tracheal bronchitis	Strep. viridans, M. catarrh., H. influenzæ	3	+	
10. E. H.	Tracheal bronchitis	Strep. viridans and nonhemol. strep., Staph. albus, diphtheroids	2	+	
11. J. T.	Pulm. suppuration (lt.)	No specimen	4	+	
12. L. S.	Pulm. abscess (rt. low.)	Strep. viridans, hemolytic strep. and H. influenzæ, Staph. albus	2	+	
13. M. R.	Pulm. abscess (lt. low.)	No specimen	2	+	
14. A. R.	Bronchiectasis	No specimen	4	+ (Discharged cured)	
15. F. A.	Bronchiectasis and lung abscess	No specimen	2	+ (Discharged cured)	
16. M. O.	Bronchiectasis	Strep. viridans, pneumococcus	5	+	
17. W.	Bronchiectasis	No report	3	+	
18. M. Mc.	Bronchiectasis	Strep. viridans, pneumococcus	3	+	

Conclusion. 1. An active polyvalent staphylococcus bacteriophage, such as prepared by us, is of apparent value when applied bronchoscopically in the treatment of bronchopulmonary suppuration.

2. Drainage is facilitated by its use, as it changes the character and quantity of the secretion.

3. This being a preliminary report, continued observations should be made to confirm the above findings.

Dr. Love wishes to express his appreciation for the association made with Professor Felix d'Herelle and Dr. Morris L. Rakieten while learning much of this technique. It was through the kindness of Prof. d'Herelle and Dr. Rakieten that he received the original stock strains of bacteriophage mentioned in this paper.

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FOREIGN PROTEIN THERAPY.

I. Hemocytologic Changes Following the Intravenous Injection of Killed Typhoid, Paratyphoid "A" and Paratyphoid "B" Bacilli.

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The changes in the cytology of the circulating blood due to the injection of foreign proteins into the circulation has received scant attention when one considers the vast amount of foreign protein therapy that is employed at the present time. With the development of our knowledge of the cytologic alterations of the blood it has become apparent that the reaction of a patient to an infection or to an intravenous injection of foreign protein is reflected in most instances by such cell changes.

History. For centuries it has been known those with chronic disease are occasionally benefited by an intercurrent acute infection. In more recent times it has been observed that such diseases as typhoid, typhus, cholera, smallpox, erysipelas and measles often left a patient suffering from a chronic luetic or tuberculous infection markedly improved. With this in mind, Fehleisen cultured streptococci from a case of erysipelas and then injected them locally in a patient with lupus. The results were remarkable in that the patient was apparently cured. In 1886, Emmerich cured a case of anthrax with a similar culture. Specific therapy, however,

occupied the foreground until Ichikawa, in 1914, found that patients suffering from paratyphoid fever responded to injections of killed typhoid bacilli as well as patients with typhoid fever. Vaccines from colon bacilli were used by Kraus and Mazza with success in cases of typhoid fever. Ludke, in 1915, demonstrated that the course and symptoms of typhoid fever could be aborted by the intravenous injection of proteose. Following the use of proteose, the term "protein therapy" was coined.

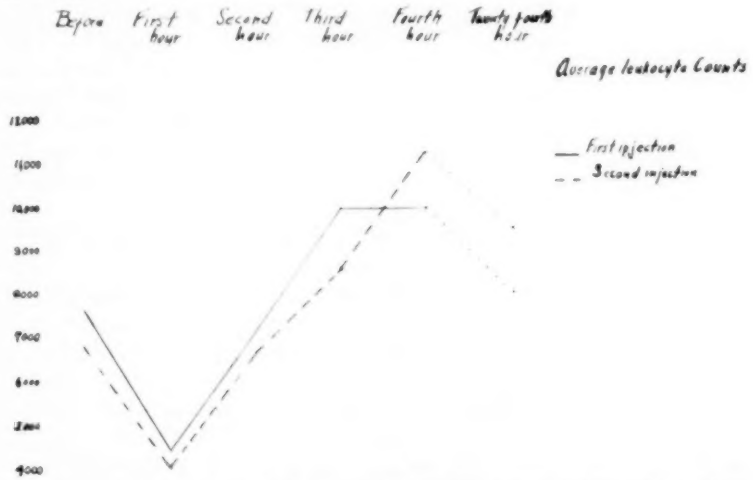
A number of references are found in the literature relative to the results obtained from the intravenous administration of foreign proteins. Whenever the investigators made examinations of the formed elements of the blood, certain alterations were consistently reported. Vaughn, as early as 1892, noted that a leukocytosis followed the subcutaneous injection of nuclein. His observations were confirmed by Brown and Ross, who found there was always a leukocytosis 4 to 10 hours after an intramuscular injection of sodium nucleinate. In their series the counts went as high as 23,000 and returned to normal in from 3 to 5 days. Cowie and Calhoun report a series of 10 patients treated with intravenous injections of killed typhoid bacilli. They observed that such an injection almost invariably initiated a leukopenia which was followed by a leukocytosis, due chiefly to an increase in the granular leukocytes. In the latter paper, attention is also called to the fact that there is a stimulation of the mesenchymal fundaments which is expressed by the presence of myelocytes and nucleated red cells in the circulation.

Methods and Materials. In the 28 patients studied, the diagnoses may be roughly classified as follows: Focal infection with acute manifestations, 17; and focal infection with chronic manifestations, 11. There were 15 males and 13 females. Of the 28 patients, 16 received a second injection of killed organisms on an average of 4.7 days after the first injection. In this group there were 9 patients with focal infection with acute manifestations and 7 with focal infection with chronic manifestations. Divided as to sex, there were 10 males and 6 females.

In each case a control count was made immediately preceding the injection. In many instances a blood count 12 to 24 hours preceding the injection had been obtained, but such counts have been considered only as checks on the control counts. Following the injection of the killed typhoid and paratyphoid bacilli a complete blood count was made at hourly intervals for a period of 4 hours. Twenty-four hours after the injection another complete blood count was taken. With few exceptions the blood counts were made by the same person, and the differential count in all instances was checked by one of us. In the differential counts particular attention was paid to the immature forms, and on the original protocols the Schilling count and shift were recorded.

The bacterial vaccine used was Eli Lilly and Company's V-765, each cubic centimeter containing killed typhoid bacilli, 1000 million; paratyphoid bacilli A, 500 million; and paratyphoid bacilli B, 500 million.

The first dose of vaccine injected intravenously averaged 0.075 cc. per patient, an equivalent to 75 million killed typhoid bacilli, 37,500,000 killed paratyphoid A and 37,500,000 killed paratyphoid B bacilli. In the group of patients receiving a second injection of killed organisms, the average dose was 0.15 cc., which represented 150 million killed typhoid bacilli, killed paratyphoid A and B, each 75,000,000. The maximum dose was 0.2 cc. and the minimum 0.05 cc.



GRAPH I.—Average total leukocyte counts following the first and second injections of killed organisms.

Observations. Graph I shows the average total leukocyte counts following the first and second injections of killed organisms. The similarity of the two curves is most striking. In this graph there is not an actual leukopenia represented, as the control count of 20 patients showed a total leukocyte count of over 5000. A drop in the leukocyte count occurred in 21 of the 28 cases, with an average decrease of 4665; whereas 6 gave an average increase of 99.1. In one examination the count remained the same. Upon comparing the results obtained at the end of the first hour following the first and second injections, no consistent individual reaction was found, and the size of the dose administered did not seem to influence the count.

In the second hour there occurs following both injections a recovery from the relative leukopenia to almost the pre-injection count. In this hour's counts we find following both the first and

second injection 5 patients with a decrease in their leukocyte count. Of this number there was only 1 who showed a decrease in both the first and second hours.

The third hour counts gave a continued increase. There was approximately the same number of patients whose counts opposed the general trend as was observed in the preceding 2 hours. The maximum total leukocyte count following the first injection of killed organisms occurred in this hour's count.

In the fourth hour the count following the first injection remained the same, whereas following the second injection the maximum count was obtained. Again a small percentage of the counts showed a decrease.

One more series of counts was obtained 20 hours later, or 24 hours after the injection of the killed organisms. In both curves there was a decrease in the total leukocyte count, the counts following the first injection dropping to a lower level than those following the second. After both injections the final counts were higher than the control counts. At the end of 24 hours there was again a discrepancy in that a few patients showed an increased leukocyte count over the count immediately preceding.

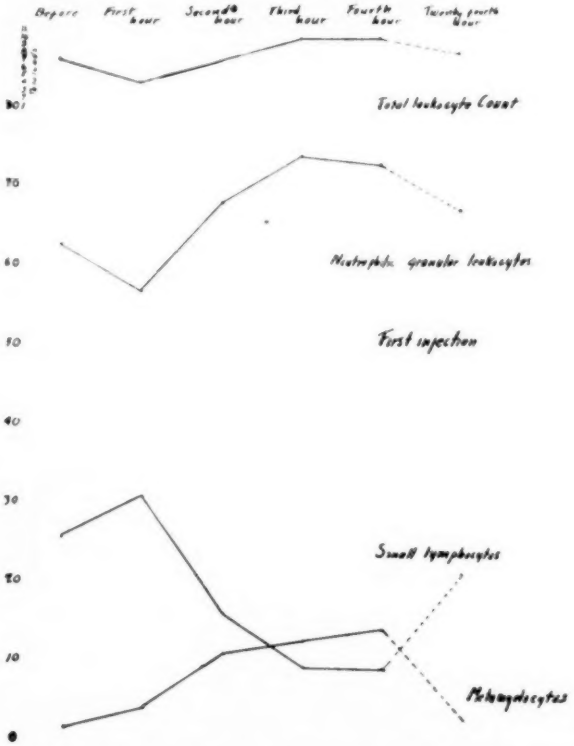
Following each injection of killed organisms the blood studies consisted of hemoglobin determinations, a count of the red blood cells, white blood cells, color index and a complete differential count. The only significant findings occurred in the leukocyte count and in variations in the number of neutrophilic granular leukocytes, small lymphocytes and metamyelocytes.

On Graph II are shown the total leukocyte count, the average neutrophilic granular leukocytes, the small lymphocyte and the metamyelocyte count, the latter 3 expressed in percentage. The counts from which these curves were plotted were obtained after the first injection of killed organisms.

It will be recalled that 28 patients were examined in this group and that the total leukocyte count was discussed in a preceding paragraph. The trend of the total leukocyte counts, the neutrophilic granular leukocyte and the metamyelocyte counts is most striking. The period of relative leukopenia corresponds with a decrease in the number of neutrophilic granulocytes, although during this period the metamyelocytes definitely increased. In almost every instance the metamyelocyte increase preceded the neutrophilic granulocyte increase by 1 hour. The maximum degree of increase of the metamyelocytes always occurred during the second hour, although the maximum percentage was not attained until the fourth hour. Comparing the neutrophilic granular leukocyte and metamyelocyte curves it is noted that they are almost parallel except during the first hour.

The curve representing the lymphocyte count is quite consistent. This type of cell increases in number during the period of leukopenia,

but rapidly falls to below normal level as well as the control level during the second, third and fourth hours. The upward trend occurs between the fourth and twenty-fourth hours, but the final count does not equal the control. In addition it will be noted that this curve is just the reverse of that of the neutrophils and total leukocyte count.



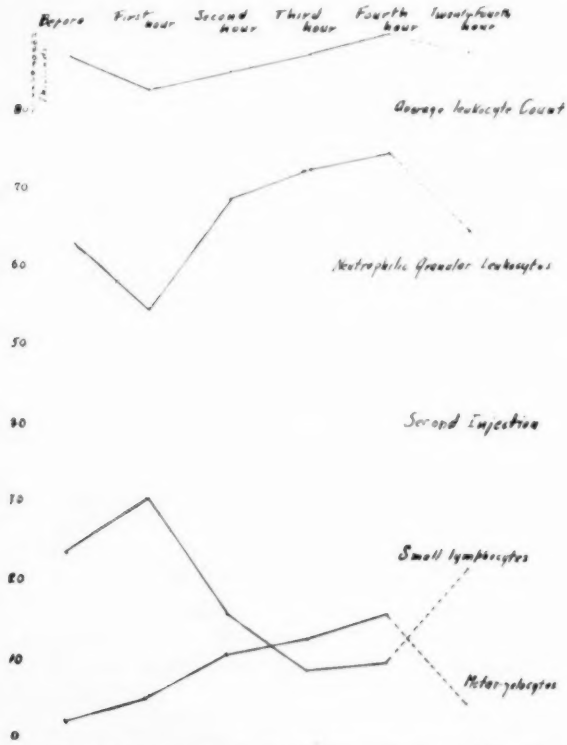
GRAPH II.—The total leukocyte count, the average neutrophilic granular leukocyte, the small lymphocyte and the metamyelocyte counts following the first injection of killed organisms.

In all the examinations there were counts whose trends were at variance with the majority, but in no instance did this variance persist in the same patient. This statement in turn holds true for the next group.

Of the 28 patients previously discussed, 16 had a second injection of vaccine. Graph III represents as before the average total leukocyte count and the average percentage of neutrophils, small lymphocytes and metamyelocytes. The trends of these curves are identical with those following the first injection, and it is noticeable

that the total count varies little even though the average dose is almost doubled.

Of most interest to us in the study of these differential cell counts were the cells of the myeloid series. As has been previously mentioned, the neutrophilic granular leukocytes closely followed the total leukocyte curve and at the peak of the curve many young adult granular leukocytes were found. The immature forms of the myeloid series that had made their appearance early in the reaction



GRAPH III.—The total leukocyte count, the average neutrophilic granular leukocyte, the small lymphocyte and the metamyelocyte count following the second injection of killed organisms.

reached their maximum number at the same time. These immature forms were, with the exception of 2 instances, all metamyelocytes of the neutrophilic type.

In the 220 blood counts studied, 5 myelocytes were found, and these occurred in 2 patients following the first injection. In 1 patient there was found 1 myelocyte in the third, and 3 in the fourth hour. The remaining cell was found in the 24-hour count of the second patient.

Our findings in this respect differ from those of Cowie and Calhoun who report that myelocytes were found quite regularly after injection in 24 out of 29 reactions. In their series they also observed that nucleated red cells were found in 7 out of 10 cases, while in our series they occurred in only 2 examinations. As the total number of nucleated red cells found was only 3, and as 2 of these were in the same count, we do not consider their presence significant.

Discussion. Many theories have been advanced to explain the results that occur following intravenous foreign protein medication, but no theory has been generally accepted. It is thought that the beneficial results obtained are due primarily to a strengthening of the immunogenic system of the body. Resistance or immunity is dependent upon the formation of substances known as antibodies. Phagocytosis of invading organisms by certain strains of leukocytes is another important factor in the recovery of a patient from bacterial disease, in fact, in discussing the subject of resistance, immunity and phagocytosis cannot be separated. Where antibodies are formed has been the subject of much experimental work, and the most generally accepted theory is that some antibodies are formed locally, while others appear to be formed simultaneously throughout the body. In the literature suggestions are found that the reticuloendothelial system is the site of formation of these substances, but such an activity has not been satisfactorily demonstrated. Piney states that "The failure to obtain decisive results is doubtless due in part to the impossibility of completely ablating the function of the cell and so reducing the formation of these substances."

Inasmuch as neutrophilic granular leukocytes are phagocytes and, if one adheres to the view held by the monophyletists, that these cells originate from fixed cells that are known to have phagocytic powers, it may be inferred that there has occurred a stimulation of the reticuloendothelial system with the resulting formation of new phagocytic forms and a more rapid phagocytosis of the offending organisms. On the other hand, if the reticuloendothelial system is the site of the formation of antibodies the stimulation that it has received may have resulted in the production of more immune bodies. Judging from the type of immature cells that are found in the circulation following injections of foreign proteins, such a stimulation has occurred, and the beneficial results that the patients received may be due to either one of the two previously mentioned factors, although fever and vasomotor dilatation may also be important.

In this paper we do not attempt to prove that the beneficial results obtained are due either to the phagocytic action of the leukocytes or to an increase in the immunogenic substances in the body. We do not think, however, that the increase or decrease in the number of the leukocytes, especially the granular type, does indicate the degree of reaction of the reticuloendothelial system to the foreign protein injected.

Conclusions. 1. The significant hemocytologic changes following intravenous typhoid vaccine therapy are found in the leukocyte count, the neutrophilic granular leukocytes, metamyelocytes and lymphocytes.

2. Following the injection of the killed organisms a relative leukopenia occurs in the first hour followed by a return to pre-injection level in the second hour. In the third and fourth hours there is a leukocytosis, followed by a drop to almost pre-injection level at the twenty-fourth hour.

3. The neutrophilic granular leukocyte response closely parallels the response of the total leukocytes.

4. The metamyelocytes show no initial decrease but a steady increase during the first 4 hours; their number at the end of 24 hours is practically normal.

5. The lymphocytes show an increase in the first hour with a decrease in the following 3 hours. The 24-hour count shows an increase to near pre-injection level.

6. These hemocytologic changes are transient, as evidenced by the fact that the counts at the end of 24 hours had returned to the pre-injection level.

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A STANDARDIZED TECHNIQUE FOR THE BLOOD SEDIMENTATION TEST.

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In the description of a technique for the macroscopic examination of blood, it was elsewhere[1] stated that the hematocrit employed could be used not only for the determination of volume of packed

red cells, volume of packed white cells and platelets, and of icterus index, but also for the determination of sedimentation rate. The introduction of this hematocrit for the latter purpose, in spite of the fact that a great variety of sedimentation tubes is already available, is justified because this instrument may be employed with little additional effort for the other purposes mentioned and because the sedimentation rate may, by the determination of the volume of packed red cells in the same instrument, be very readily corrected for degree of anemia. It has been repeatedly demonstrated[2,3,4,5] that a reduction in the number or mass of red corpuscles of itself leads to a decreased suspension stability of the blood, and that allowance must be made for this factor in determining the true sedimentation rate of the red corpuscles.

Various investigators have shown[2,5,6] that a number of factors influence the sedimentation rate of erythrocytes. The following studies were made with the purpose of evaluating these factors as influencing sedimentation of red corpuscles in the hematocrit used by us[1] and with the object of defining the conditions under which this instrument should be employed.

Probable Error of the Determinations. With the object of determining with what precision sedimentation readings may be made on the same sample of blood, 9 experiments were carried out, in each of which 6 hematocrits were filled with blood and read at the end of 1 hour. The sedimentation rate of these bloods ranged from 2 mm. to 69 mm. The standard deviations of the readings in each experiment ranged from 0.13 to 0.89 mm. and averaged 0.48 mm. It may, therefore, be concluded that determinations in different tubes must be considered as not significantly different unless their difference is greater than 2 mm., which represents more than twice the greatest observed standard deviation.

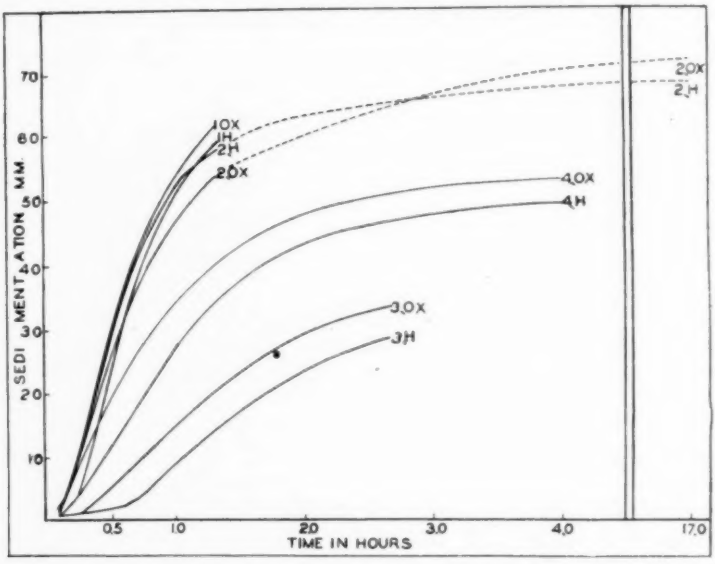
Effect of Anticoagulant. Rourke and Plass[6] showed that heparin does not alter the sedimentation rate of red corpuscles. Consequently the influence of dry potassium oxalate, 2 mg. per 1 cc. of blood, which is the amount of anticoagulant recommended for use with the hematocrit,[1] was studied by comparing the sedimentation of blood collected in this way with that of blood collected in heparin (2 mg. per 5 cc. blood). A measured quantity of venous blood was mixed with potassium oxalate while another portion of the same blood was mixed with heparin. In 4 experiments the sedimentation rate of the samples was measured at 5-minute intervals for 1 hour, and at hourly intervals thereafter (Fig. 1); in 15 experiments readings were made at hourly intervals for 3 hours (Fig. 2).

Contrary to the contention of Rourke and Plass,[6] we have found that potassium oxalate in the quantities employed is a satisfactory anticoagulant and does not depress the rate of settling. There was, on the whole, very good agreement, as Figures 1 and 2 indicate, between the sedimentation as recorded in oxalated blood and that in

heparinized blood. This was as true for readings made at the end of 2 and 3 hours as after 1 hour.

The disagreement between our observations and those of Rourke and Plass can probably be accounted for in part by the somewhat lower concentration of oxalate which we have used (10 as compared with 14 mg. per 5 cc.). We have, however, failed to note a consistently depressing effect on sedimentation even of greater quantities of potassium oxalate (Fig. 3) such as these investigators describe.

FIG. 1.—SEDIMENTATION RATE OF BLOOD COLLECTED IN SOLID POTASSIUM OXALATE (10 MG. PER 5 CC. OF BLOOD) COMPARED WITH THAT OF BLOOD COLLECTED IN HEPARIN (2 MG. PER 5 CC. BLOOD).



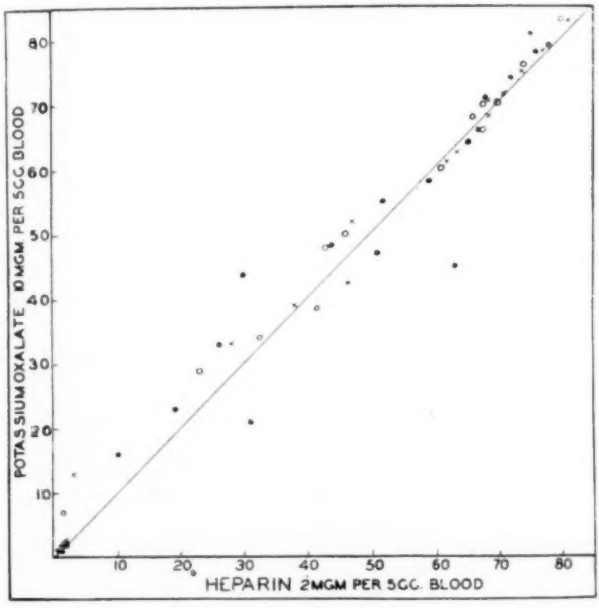
Curves to be compared are numbered 1.OX and 1.H, 2.OX and 2.H, etc. During the first hour of sedimentation, readings were made at 5-minute intervals.

Following the suggestion of Heller and Paul* we have commenced to employ as an anticoagulant for human blood, a mixture of ammonium oxalate and potassium oxalate (6 mg. of the former and 4 mg. of the latter per 5 cc. blood). In these proportions no difference in the volume of packed red cells as compared with the volume in heparinized blood has been noted and, consequently, no correction for shrinkage is necessary. In a series of experiments the sedimentation rate of blood collected in this new anticoagulant mixture agreed, within limits of technical error, with that of heparinized blood both when readings were made at 5-minute intervals and when only at the end of 1 hour.

* J. Lab. and Clin. Med., **19**, 777, 1934.

Influence of Bore and Length of Tube. From a large sample of blood collected in potassium oxalate in the concentration of 10 mg. per 5 cc., a series of tubes of different lengths and bores was filled and sedimentation readings were made during the same period of time and under similar conditions. This experiment was repeated 7 times. The results, shown in Table 1, indicate that length of tube is a factor in influencing the sedimentation of erythrocytes. As was to be expected, the longer the tube, the greater was the distance traversed by the sedimenting red corpuscles. It must be observed,

FIG. 2.—CORRELATION OF SEDIMENTATION RATES OF BLOOD COLLECTED IN SOLID POTASSIUM OXALATE AND IN HEPARIN.

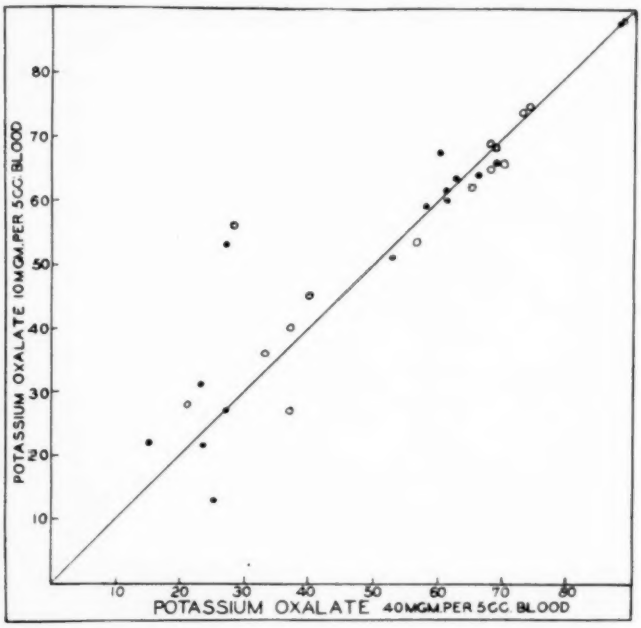


The solid circles represent readings at the end of 1 hour, the open circles readings at the end of 2 hours, and the crosses readings at the end of 3 hours. The averages of all the readings at the end of these periods of time for oxalate and for heparin, respectively, were 43.5 and 42.6 mm., 48.9 and 47.2 mm., 54.7 and 52.6 mm.

however, that distance traversed was not directly correlated with distance to be traversed, for in the tube 300 mm. in length (No. 4) the sedimentation was only slightly greater than in tubes one-third this length (Nos. 1 and 5). In fact, the readings at the end of the first hour in Nos. 1, 2, 4 and 5 were quite similar and in all but the longest tube (No. 4) this similarity was present, though to less extent, in the 2d and 3d hours. In contrast to the continuing sedimentation after the 1st hour in the longer tubes (Nos. 4, 1, 5 and 2) it is of interest to note that in the shortest tubes (Nos. 3

and 6), little further change took place after the 1st hour, the "stage of packing"[7] having apparently been reached.

FIG. 3.—CORRELATION OF SEDIMENTATION RATES OF BLOOD COLLECTED IN LOW AND IN RELATIVELY HIGH CONCENTRATIONS OF SOLID POTASSIUM OXALATE.



The solid circles represent readings at the end of 1 hour, the open circles at the end of 2 hours. The averages of all the readings at the end of these periods of time for 10 mg. and for 40 mg. oxalate, respectively, were 49.9 and 47.9 mm., 56.9 and 55.2 mm.

TABLE 1.—EFFECT OF BORE AND LENGTH OF TUBE.

Time in hours.	Sedimentation in millimeters.															
	Tube: 1*		2		3		4		5		6		7		8	
	L 100	B 2.5	L 70	B 2.5	L 35	B 2.5	L 300	B 6.0	L 100	B 6.0	L 35	B 6.0	L 40	B 4.5	L 40	B 11.0
1	31.0		26.0		17.0		35.0		28.5		17.0		21.0		20.0	
2	45.5		36.0		19.5		75.0		43.0		20.0		28.0		27.0	
3	58.5		45.0		21.0		104.5		50.5		22.0		30.0		29.5	

L and B represent length and internal diameter, respectively, in millimeters.
* Author's hematocrit.

Within the ranges observed, namely, 2.5 to 11 mm., it does not seem that the bore of the sedimentation tube is of significance when columns of blood of equal height are compared. It has been pointed

out, however,[5,8] that tubes less than 2 mm. in internal diameter are unsatisfactory because sedimentation is uneven in such tubes.

Inclination of the Tube. It has been repeatedly demonstrated[8,9,10] that a deviation of the sedimentation tube from the perpendicular position causes an acceleration of the sedimentation rate. From our own observations (Table 2) in a tube 100 mm. in length, it appears that an inclination of as little as 2.3% causes an acceleration of 30%. The physical basis for the increased sedimentation rate in inclined tubes is clearly explained by Ponder.[9]

TABLE 2.—INFLUENCE OF INCLINATION OF TUBE.

Inclination of tube.	Vertical.	0.4°	1.0°	2.0°	2.3°	3.0°	4.0°	5.0°	6.5°	10.0°	15.8°	16.0°	23.5°
Sedimentation in 1 hour, mm.	30.0	29.0	....	....	39.0	....	....	....	....	44.0	....	43.0	
Sedimentation in 1 hour, mm.	17.0	....	17.5	17.0	....	22.0	24.0	25.5	....	....	....	....	....
Sedimentation in 1 hour, mm.	10.5	....	....	....	....	....	....	....	14.0	....	30.0	....	31.5
Error due to inclination, per cent	....	3	3	0	30	29	41	50	33	47	186	43	200

Effect of Temperature. All observers[6,11,12] agree that the temperature of the room or receptacle in which the sedimentation test is carried out influences the sedimentation rate, there being increased settling with rising temperature. Our own experiments, carried out under controlled conditions and in carefully regulated water baths, show a consistent increase in rate as temperature rises. In Table 3, the means for 10 experiments on bloods with sedimentation rates ranging (at 22° C.) from 2 to 55 mm. are shown.

TABLE 3.—EFFECT OF VARIATIONS IN TEMPERATURE.

Temperature C.	10°	15°	20°	21°	22°	23°	24°	25°	26°	27°	28°	29°	30°	31°	32°
Sedimentation mm. in 1 hour	9.0	19.0	32.6	33.0	33.4	33.9	35.1	35.7	37.6	35.9	37.1	37.6	37.6	38.6	40.2

Westergren[11] has suggested that a correction of the sedimentation rate be made for the influence of temperature. Since the differences within the average range of temperature of most laboratories are small, it seems more practical to carry out the test in a room temperature of 22° to 27° C., modifications in technique being made only when temperature conditions are unusual. The effect of differences in temperature must be borne in mind particularly when the sedimentation readings are near the limit of normal or when the progress of a patient is being followed from time to time by means of this test.

Changes in Suspension Stability of Blood as Influenced by Delay in Carrying Out the Test. It has been stated[6,11,13] that a specimen of blood may be allowed to stand at room temperature for several hours without changing its suspension stability. We have found, however, that after 4 hours significant differences occur although in some instances these have not been noted sooner than 6 hours after the collection of the blood. Delay causes a decrease in the sedimentation rate. We have found no changes in sedimentation rate in samples of blood kept in a refrigerator (9° C.) and subsequently warmed to room temperature as long as the test has been carried out within 4 hours of the drawing of the blood.

Miscellaneous Factors Which Appear to Exert No Significant Influence on Sedimentation Rate. Under this head may be included: (i) the specific gravity of the red corpuscles themselves,[14] or their size;[14] (ii) aëration of the blood or loss of carbon dioxid;[6] (iii) the collection of blood from arteries or veins;[15] (iv) centrifuging the blood and subsequently remixing the cells and plasma;[6] (v) the ingestion of food,[6] and (vi) short violent exercise.[6]

The Concentration of the Suspension. It has been repeatedly demonstrated[2,4,6,13,16,17,18] that the concentration of the blood is a very important factor in influencing the sedimentation rate, the more dilute the blood the greater being the speed of settling. Fåhraeus[19] has pointed out that this relation is not direct or linear, there being, *cæteris paribus*, less tendency to aggregate in blood sparse in red corpuscles. The influence of concentration has been shown to be so great, that a number of investigators have recommended that the observed sedimentation rate be corrected for the degree of dilution (anemia) or concentration (polycythemia) of the blood. This may be done by taking into account the red cell count,[5] the hemoglobin content[20] or the volume of packed red cells.[3,21]

By far the simplest procedure is to make a correction according to the volume of packed red cells for, if the hematocrit is used for determining sedimentation rate, all that is required is centrifugation of the tube after the sedimentation rate has been determined.

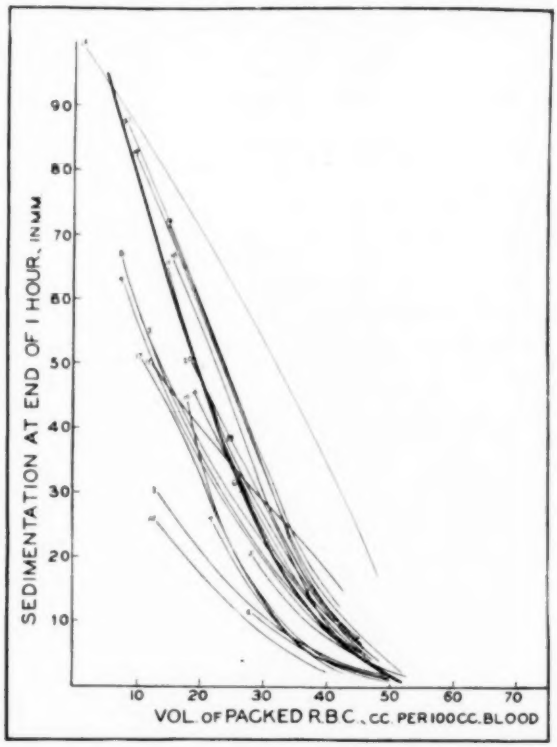
Rourke and Ernstene[3] have prepared a chart for correcting the sedimentation rate as judged by the "period of constant sedimentation" or period of most rapid fall and have devised a "corrected sedimentation index." Their chart may be satisfactorily employed in connection with the hematocrit employed by us for this instrument is of the same length and only of slightly less inside diameter than the tube of Rourke and Ernstene.

The determination of the "corrected sedimentation index" of Rourke and Ernstene requires the recording of degree of settling at frequent intervals. This may be satisfactorily done by photographic means,[22] but the requisite apparatus is not available to every laboratory, and to read the degree of sedimentation every few minutes requires time and seriously detracts from the simplicity

which is the outstanding merit of the sedimentation test. Consequently it was thought advisable to prepare a chart which would serve to correct the sedimentation rate as read at the end of 1 hour.

Data for the preparation of a correction chart were obtained as follows: A large sample of blood was collected in solid potassium oxalate, 10 mg. per 5 cc. of blood. The sedimentation rate of this

FIG. 4.—CORRELATION OF SEDIMENTATION RATE AND VOLUME OF PACKED RED CELLS.



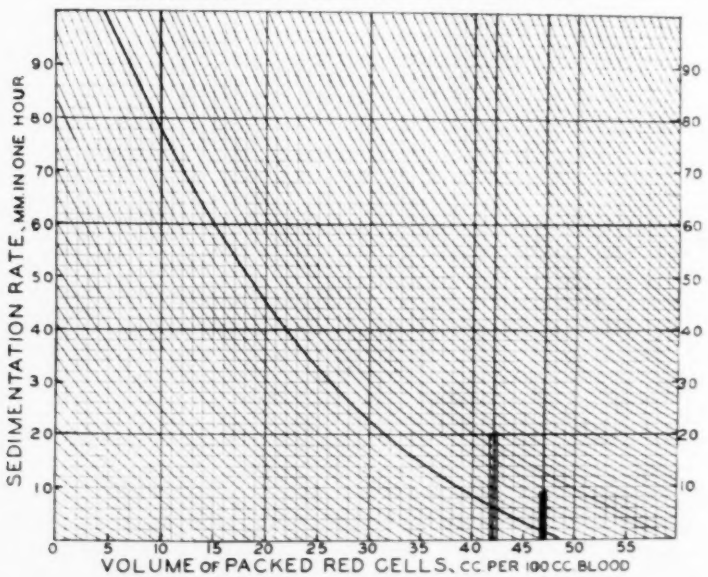
Each curve represents an experiment in which successive dilutions of blood were made with plasma and sedimentation rate was determined for each sample so prepared. Curves 1 to 13 are derived from the blood of normal men, Curves 14 to 21 are from the blood of normal women. The curve outlined most heavily is a logarithmic curve based on these observations.

blood and the volume of packed red cells were determined. Subsequently, the blood was diluted with increasing quantities of its own plasma and the rate of settling and volume of packed red cells were determined on each sample of diluted blood. In this way 6 to 9 dilutions were made with each sample. The determinations were made under the conditions already outlined as necessary for the accurate performance of the sedimentation test. Twenty-one

experiments were carried out in this way. The blood was obtained from 13 normal men and 8 normal women. The sedimentation rates in these experiments varied from 1 to 98.5 mm. in 1 hour and the volume of packed red cells ranged from 52.5 to 1.5 cc. per 100 cc. of blood. The curves for each of these bloods are shown in Figure 4.

Analysis of these data revealed a high degree of correlation between sedimentation velocity and volume of packed red cells, the lower the latter, the greater being the rate of settling. The correlation coefficient was $-.8642 \pm .0127$. Comparison with the correlation ratio which was .9202 showed, however, that the correlation was non-linear, ζ being $.1600 \pm .0304$.

FIG. 5.—CHART FOR CORRECTING SEDIMENTATION RATE FOR VARIATIONS RESULTING FROM DIFFERENCES IN THE CONCENTRATION OF RED CORPUSCLES AS MEASURED BY VOLUME OF PACKED RED CELLS.



The logarithmic curve on which the chart is based is heavily outlined. The mean normal volume of packed red cells for men (47 cc.) and for women (42 cc.) are also heavily outlined and the range of normal sedimentation is represented by solid and open columns for each sex, respectively.

Since the correlation for the data obtained for male blood ($-.8970 \pm .0132$) was not very different from that obtained for female blood ($-.8680 \pm .0196$) and since the individual curves for the two sexes did not seem to differ, all the data obtained were utilized for the preparation of a corrective curve. A logarithmic curve of the formula, $y = 44.97 - 1.37x - 23.4 \log x$, was found to best fit the observations.

A correction chart which has been prepared on the basis of this curve is shown in Figure 5. An example will serve to explain how the chart may be used.

Let it be supposed that the sedimentation rate of the blood of a female patient is 40 mm. in 1 hour and that the volume of packed red cells is 25 cc. per 100 cc. of blood. The horizontal line at 40 on the chart is followed to the right as far as the point at which the vertical line rising from 25 meets it. The curved line nearest this point is then followed downward and to the right, as far as the normal line for volume of packed red cells in women. It is found that the curve in this instance meets the normal line opposite 11 mm. Consequently the "corrected" sedimentation rate is 11 mm. This is well within the range of sedimentation in the blood of normal women. It is assumed that the original sedimentation rate of 40 mm. is no greater than would be expected if the blood of a normal woman had been diluted to 25 cc. of packed red cells per 100 cc. blood. However, if the sedimentation rate for this blood had been found to be 70 mm. while the volume of packed red cells remained the same (25 cc.), the corrected sedimentation rate would be 30 mm. Since this is distinctly greater than normal, the inference is drawn that the sedimentation rate of this blood is greater than can be accounted for by the anemia alone.

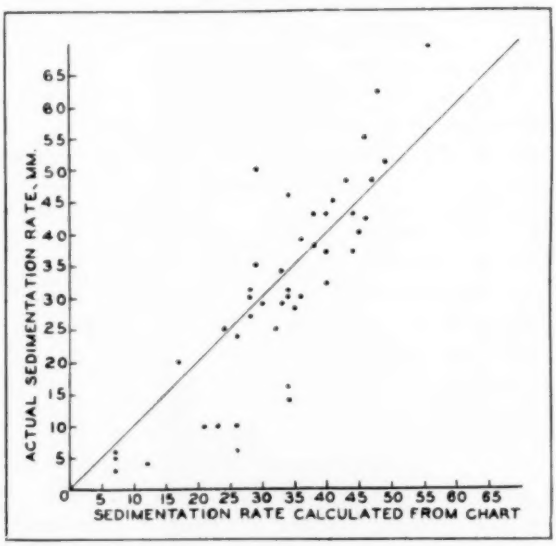


FIG. 6.—CORRELATION OF ACTUAL AND CALCULATED SEDIMENTATION RATES. CORRELATION COEFFICIENT, .7950 ± .0272.)

The accuracy of this chart was tested in the following manner. Blood was obtained from a series of 31 patients suffering from a variety of ailments and having various grades of anemia. Sedimentation rate and volume of packed red cells were determined. The blood was then concentrated by withdrawing plasma, and sedimentation rate and volume of packed red cells were again determined.

Frequently this procedure was repeated and thus a total of 45 determinations were carried out. In Figure 6 the relation of the sedimentation rate actually found after concentration of the blood, is compared with the sedimentation rate calculated for the original sedimentation rate and volume of packed red cells at the level of packed red cells found in the concentrated blood. It will be seen that the correlation, although not perfect, is nevertheless quite high.

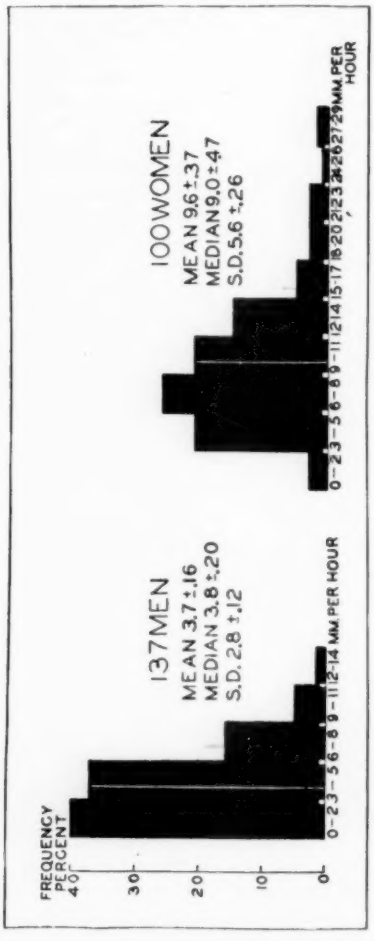


FIG. 7.—FREQUENCY DISTRIBUTION OF SEDIMENTATION RATE IN 137 MEN AND 100 WOMEN.

Sedimentation Rate in Normal Adults. Blood was obtained from 137 men and 100 women. The men were medical students who had received a complete physical examination 1 to 4 months prior to the blood examination. As far as can be judged by history, physical examination, roentgenograms of the chest, blood counts and Was-

sermann tests, these men were in excellent health and none suffered from even a mild infection at the time of blood examination. The women included a number of medical students but were chiefly nurses. With the exception of roentgenograms of the chest, the latter were judged to be in good health by the same tests as the medical students. The sedimentation test was carried in the manner already outlined[1] and the precautions already considered were observed. Red cell counts, hemoglobin and volume of packed red cells were determined on the same samples of blood and these have been reported elsewhere.[23]

The frequency distribution as well as other statistical data for these observations are presented in Figure 7. It will be noted that the mean for men is much lower than that for women and also that the variation in sedimentation rate in the latter is much greater than among the men. The variation observed in the men was only slightly correlated with volume of packed red cells, the correlation coefficient being $-.2334 \pm .0545$. Among the women no correlation was observed between sedimentation rate and volume of packed red cells, the correlation coefficient being $-.0258 \pm .0650$.

The data available do not afford any evidence concerning the cause of the wide variation in sedimentation rate in the women. The date of the last menstrual period was recorded when the blood was drawn for the sedimentation test but the information gathered fails to reveal significant information. The mean sedimentation rate during the first postmenstrual week was 10.2 mm.; during the 2d week, 9.3 mm.; during the 3d, 8.6 mm., and during the 4th week 10.9 mm. Although these figures show somewhat higher values in the weeks immediately preceding and following menstruation, the differences are too small to permit conclusions to be drawn. Greisheimer[24] noted a greater variation in sedimentation rate in women as compared with men but did not find that this was related to the menstrual periods as earlier observers had suggested.

In setting the maximum limits of normal variation in sedimentation rate, it is probably quite adequate to consider the mean value plus or minus twice the standard deviation, since this includes 95.45% of all the variates. This would set the limit of normal in men at 0 to 9 mm., and in women 0 to 20 mm. In the great majority of normal men sedimentation rate should really be no greater than 6.5 mm., and in women no greater than 15 mm. These values represent 86.4% of all the variates observed.

Summary and Conclusions. The influence of various factors on the suspension stability of the blood has been studied, conditions for its accurate performance have been considered, and the normal sedimentation rate under these conditions determined.

The use of a special hematocrit is recommended for the determination of the sedimentation rate because the same instrument can be used subsequently for the measurement of volume of packed red

cells, volume of packed white cells and platelets, and icterus index. The determination of volume of packed red cells is especially valuable because by this means the sedimentation rate may be corrected for alterations due to anemia.

The following appears to be a satisfactory and accurate method of procedure:

Method. 1. Five cc. of venous blood is collected by means of a dry syringe and needle and mixed in a small bottle containing 4 mg. solid potassium oxalate and 6 mg. solid ammonium oxalate. This concentration of oxalate does not alter the sedimentation rate as compared with that of blood collected in heparin. Less than 1 cc. of blood is needed for the sedimentation test. The remainder can be used for other blood examinations.

2. The blood so collected should be used for the determination of sedimentation rate within 4 hours of its time of collection. Further delay may be associated with increased suspension stability of the blood.

3. The hematocrit is filled to the 10 cm. mark with blood. The upper level of sedimenting corpuscles may be read at frequent intervals or, more simply, a single reading may be made at the end of 1 hour.

4. Since sedimentation rate increases with increasing temperature, the sedimentation test should be carried out at a temperature not less than 22° nor greater than 27° C. Within this range variations resulting from differences in temperature are small. If the blood used has previously been kept in a refrigerator it should first be permitted to attain the above temperature before being used.

5. The hematocrit should be kept in an exact vertical position during the sedimentation of the blood corpuscles, for when the instrument stands at an angle of even 3° from the vertical, significant acceleration of sedimentation takes place.

6. After sedimentation rate has been determined, the hematocrit containing the blood should be centrifugalized and volume of packed red cells determined. The sedimentation rate may then be corrected for alterations due to anemia. A correction chart is presented.

The average sedimentation at the end of 1 hour has been found to be, in healthy men, 3.7 mm. and, in normal women, 9.6 mm. In 86% of the men examined the sedimentation rate ranged from 0 to 6.5 mm., whereas in the same proportion of women the sedimentation rate ranged from 0 to 15 mm. In an additional 9% the sedimentation rate ranged as high as 9 mm. in men and 20 mm. in women. These values probably represent the extreme range of normal variation under the conditions outlined.

We are indebted to Mr. Wilbur Rigger for technical assistance.

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MACROCYTIC ANEMIA AND HEPATIC CIRRHOSIS.

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The not infrequent occurrence of a blood picture in hepatic cirrhosis that approaches that of pernicious anemia during remission has been widely recognized but not sufficiently appreciated. The purpose of this communication is to report the blood pictures of 12 cases of portal cirrhosis and to present the data obtained from a review of 41 case records.

The fact that the patients showing this type of blood picture do not resemble clinically pernicious anemia, plus the fact that such descriptive terms as "pernicious anemia-like blood picture" or "a blood picture that closely resembles pernicious anemia" are cumbersome, lengthy and inflexible, seems to justify the coining of an appellation such as pernicioid (pernicious-like) anemia. Therefore, this term will be used in the following discussion.

Review of Literature. Recent reports calling attention to this pernicioid, or pernicious anemia-like, blood picture have been made by Wintrobe and Shoemaker, Goldhamer, Van Duyn and others. An adequate review of a number of reports of less recent date has been presented in the article by Wintrobe and Shoemaker.[1]

Goldhamer[2] reports such a case of hepatic cirrhosis with free hydrochloric acid present in the gastric contents. Liver therapy produced a hemopoietic response similar to that observed in patients with true pernicious anemia. He suggests that an additional factor in the production of a blood picture resembling pernicious anemia may be interference with the storage of the material necessary for the maturation of red blood cells.

Van Duyn[3] reports 4 cases: 1 of hepatic cirrhosis, 2 with hepatitis and cirrhosis and 1 with chronic diffuse and acute hepatitis. Free hydrochloric acid was present in the gastric contents of all 4 patients. In a review of 28 case records of hepatic cirrhosis he found 5 (18%) with a high color index in the presence of an anemia. He points out a group of conditions which are associated with a macrocytic type of anemia and in which diseases of the liver are outstanding features and suggests that diseases of the liver should be given a place in the mechanism of the production of a macrocytic anemia.

Wintrobe and Shoemaker[1] report 11 instances of macrocytosis in 43 cases with various hepatic disorders. There is an absence of free hydrochloric acid in 6 of the 10 patients in whom gastric analyses were performed. The presence of the extrinsic factor of Castle was demonstrated in the gastric contents of 1 of these patients. A clear-cut response to liver therapy was not observed in 3 cases, but in the 4th a maximal response of reticulocytes occurred. They suggest that this macrocytosis may be the result of the inability of the damaged liver to store the hematopoietic substance formed by the interaction of Castle's intrinsic and extrinsic factors and by a combination of partial gastric disturbance and incomplete liver damage.

Methods. The methods used have been described by Musser and Wintrobe.[4] The average of 2 hematocrit readings was used in each determination. All erythrocyte counts reported are the average of 2 counts that check within 100,000. All hemoglobin determinations were made by the Newcomer method.

Summary of 12 Cases Studied. (Table 1.) A clinical diagnosis of portal cirrhosis was made in all cases without equivocation. Additional diagnoses, when present, are given in Table 1.

The average age was 54 years (extremes, 41 and 76). Their history of alcoholic consumption varied; 6 had long revelled in the false felicities of chronic inebriety; 2 professed abstemious lives, while the remaining 4 had used strong drink in moderate or negligible quantities. Free hydrochloric acid was absent in 6 of the 8 cases in which gastric analysis was performed. The first 4 cases are of special interest because they maintained a color index above 1, in spite of the fact that the portal cirrhosis was accompanied by conditions that are commonly associated with a microcytic hyperchromic type of anemia. Clinical jaundice was absent in all cases.

The color index was more than 1 in 9 cases; the average for the entire group was 1.09, the lowest 0.81, and the highest 1.36. The mean corpuscular volume was above 90 in 7, the average was 90.1, the lowest 80.7 and the highest 96.4. The increase in color index was more constant than the increase in cell size which was at the upper limit of normal. The average erythrocyte count was 4,039,000. Two of the cases had counts above 5,000,000. The total leukocyte count was below 5000 in 5 cases, above 7500 in only 2; the average for the 12 cases was 5840. The low white cell count emphasizes

the point brought out by King,[6] that the presence of leukopenia cannot be used as a criterion for the differential diagnosis of Banti's disease with secondary cirrhosis from portal cirrhosis.

TABLE 1.—ANALYSIS OF DATA OF 12 CASES WITH MACROCYTOSIS.

Case No.	M.C.V.*	Color index.	Hemoglobin, %.	R.B.C., millions per c.mm.	W.B.C., thousands per c.mm.	Free HCl.	Ascites.	Liver.	C_2H_5OH.	Additional diagnoses.
1 . . .	95.0	1.20	89.7	3.67	3.5	0	+	+	+	Alcoholic neuritis.
2 . . .	83.4	1.36	103.0	3.76	5.5	0	+	+	+	Amebiasis.
3 . . .	92.0	1.03	82.8	4.06	11.5	6	+	−	+	Uncinariasis.
4 . . .	91.0	1.26	48.3	1.98	3.7	0	?	+	+	Tertian malaria.
5 . . .	92.6	1.06	82.8	4.26	7.5	?	+	+	0	
6 . . .	94.0	1.01	79.0	3.94	..	0	+	+	0	
7 . . .	89.0	0.87	89.7	5.01	4.5	0	−	+	?	
8 . . .	80.7	0.96	96.0	5.10	6.2	−	+	+	?	
9 . . .	95.0	1.30	97.0	3.72	5.5	22	−	+	?	Lues.
10 . . .	96.4	1.16	58.6	2.59	4.0	−	+	−	?	Arteriosclerotic heart disease.
11 . . .	89.0	1.16	110.0	4.76	4.2	0	+	+	+	
12 . . .	84.3	0.81	75.9	4.60	7.6	..	+	−	+	
Aver. . .	90.1	1.09	..	4.04	5.8					

* M.C.V. refers to mean corpuscular volume expressed in cubic microns.

Report of 41 Case Records. The records of 41 cases of portal cirrhosis admitted to the wards of Charity Hospital during the last 10 years have been reviewed in an effort to throw additional information on the incidence of macrocytosis and portal cirrhosis. The only criterion available was the color index. All hemoglobin determinations were done by the Tallqvist method, which is notoriously inaccurate.

Average age for this group was 53.5 years (extremes, 28 and 78).

Physical Findings. Ascites: ascites was present in 32 cases (62.7%). *Diarrhea:* diarrhea was present in 11 (21.5%). *Jaundice:* jaundice was present in 10 (19.6%). *Hemorrhage:* gastric hemorrhage was present in 7 (13.7%). *Tongue:* the tongue was recorded as atrophic or red in 7 (13.7%). *Blood pressure:* blood pressure was unusually low for the group, with an average age of 53.5 years. The mean systolic pressure was 121.9, and the mean diastolic, 75.4. Only 4 patients showed a diastolic pressure of 100 or more and all of these showed evidence of chronic nephritis.

Laboratory Data. Gastric analysis: gastric analysis was recorded in 18 instances; 11 patients (61.6%) showed a low figure for free hydrochloric acid; 3 of these were less than 10, the other 8 (44.4%)

showing an absence of free hydrochloric acid. *Blood picture:* the average white cell count was 7891; the average red cell count was 3,924,000. The total erythrocyte count was between 4,500,000 and 3,500,000 in 31 cases; 9 were above 4,500,000, and the remaining 3 were below 3,000,000. *Color index:* the average color index was 0.916; 14 (27.4%) showed a color index of 1 or more.

Discussion. It is of interest to see how much diagnostic value may be attached to the presence of this pernicioid anemia. Its presence has been reported in so many different conditions in which the liver is adversely affected that it cannot be expected to point out any specific lesion of that organ, but it should suggest hepatic disease. It is conceivable, however, that a slight macrocytosis and a color index of more than 1 in the presence of hematemesis may serve as a criterion to differentiate hematemesis secondary to cirrhosis of the liver, from bleeding ulcer or carcinoma.*

The first problem in estimating its diagnostic significance is to determine the frequency with which it occurs, and this cannot be done until a larger series of cases has been reported. In this limited group of 12, all but 1 (90%), with a red count below 5,000,000, showed a color index of more than unity. Judging from other reports and from the case records reviewed, it is probably only a coincidence that such a high percentage of this group should show this interesting finding.

Case 12 illustrates the pertinent fact that this blood pattern does not occur at any definite period in the progressive downward course of portal cirrhosis and that it does not depend on the degree of obstruction to the portal circulation. This patient's symptoms were of longer duration and the consequences of portal obstruction more marked than in any one of the other cases. Paracentesis had been repeated 17 times, but he did not develop a macrocytosis or high color index. His mean corpuscular volume was 84, color index 0.81 and the total erythrocyte count was 4,605,000.

When attempting to explain the etiology of this most interesting blood picture, one must remember that prodigal hypothesizing is cheap but not infrequently fallacious. The most logical hypothesis would seem to be that the portal obstruction and the concomitant gastric congestion adversely affect the formation of the nebulous intrinsic factor of Castle, but Wintrobe and Beebe have demonstrated the presence of this intrinsic factor in the gastric contents of one of their cases and, furthermore, a similar blood picture has been reported in other conditions in which there is no reason to believe that gastric function has been disturbed. Macrocytosis and a high color index have been reported in such seemingly intangible conditions as chronic hepatomegaly,[1] metastatic carcinoma of the liver,[1] acute catarrhal jaundice,[1,7] chronic passive congestion

* Hemorrhage has also been shown to increase temporarily the diameter of the erythrocyte. (See Am. J. Physiol., **103**, 407, 1933, and Quart. J. Exp. Physiol., **19**, 145, 1928).

of the liver,[1] erythroblastosis fetalis,[5] congenital syphilis,[5] arseniuretted hydrogen gas poisoning,[8] infections of the gall badder,[9] Weil's disease[7] and thrombosis of the portal vein,[7] but all of these seemingly unrelated conditions have one thing in common—that all is not well within Glisson's capsule. Therefore, the most plausible hypothesis is that disturbed hepatic function prevents the further elaboration or proper utilization of the anti-anemic substances formed by the interaction of the intrinsic and extrinsic factors.

Summary and Conclusions. 1. The blood picture in 12 cases of portal cirrhosis is reported, pointing out the tendency to macrocytosis and a high color index. Pernicioid (pernicious-like) anemia has been suggested as an appropriate term to apply to this condition.

2. A review of 41 case records of portal cirrhosis showed a color index of 1 or more in 27.4%.

3. The diagnostic possibilities of this type of blood picture have been briefly discussed.

4. Its production is attributed to hepatic abnormalities which prevent the further elaboration and utilization of the anti-anemic substances.

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INTRAPLEURAL PRESSURE IN ARTIFICIAL PNEUMOTHORAX DURING PREGNANCY AND CHILDBIRTH.*

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Valsalva (1740) observed the effect of inspiration and expiration upon the circulation and thus described what has become known as "the Valsalva experiment." "If the glottis is closed after a

* Read before The American Clinical and Climatological Association, Toronto, Canada, May 23, 1934.

deep inspiration and a strenuous and prolonged expiratory effort is then made, such pressure can be exerted on the heart and intrathoracic vessels that the movements and flow of the blood are temporarily arrested."[1]

This observation has been studied in more recent years, and through the use of modern technical procedures it has been shown by Mosler and Balsamoff:[2]

1. That there is a sharp increase in pressure in the bronchi and alveoli (Krause[3]) "because of which increased alveolar pressure the blood in the soft-walled capillaries is driven into the left heart and thence into the general circulation. A renewed influx of venous blood into the right heart cannot follow because the entrance to the right heart is narrowed by the venous trunks being compressed by the increased intrathoracic pressure. This severe pressure is transmitted not only to the lungs and bloodvessels, but also to the heart wall. As a result the complete emptying of the heart contents can occur—the heart pumping itself empty."

2. "That the diminished size of the heart during the Valsalva experiment is a real and not an apparent one due to rotation.[2] This observation has been more recently described by Moore and Wilson[4] under the name of 'cardiac squeeze.' In obstructive emphysema due to tracheal foreign bodies they found the heart measurements definitely smaller during the expiration."

Beck and Isaac[5] have shown in their studies on animals that the normal heart satisfactorily withstands exposure to atmospheric pressure, but the effect of "pneumocardiac tamponade" may persist for hours after the tamponade has been corrected and, if the heart cannot make the added effort to overcome this burden, it may after a long struggle completely fail.

With an increased intrapleural pressure the venous pressure is elevated and the circulatory rate is slowed,[6] and by increasing the intrapleural pressure in a pneumothorax the lymph flow may be reduced by as much as 50%.

The inhalation of carbon dioxid is accompanied by an increased negative intrapleural pressure, while on the other hand, in anoxemia there occurs a steadily rising pressure in the pleura, accompanied by an increase in the mean thoracic girth, as witnessed during an asthmatic attack.[8]

During the performance of an expulsory effort made with the glottis open, but blowing against resistance, it is possible to build up an intratracheal pressure of 250 mm. of mercury.[9] With the same expulsory effort made with the glottis closed, it would seem reasonable to suppose the pressure would be higher.

The involuntary occurrence of the Valsalva experiment takes place during the performance of heavy lifting or other laborious work, extreme athletic efforts, defecation and in childbirth. The

same effect occurs during severe whooping cough and stenosis of the larynx.[10]

The only reference we have found regarding the intrapleural pressure during the performance of the Valsalva experiment is by Kountz and associates,[5] but they permitted only a moderate expulsory effort—the intrapleural reading reached a positive of 12 cm. of water.

We have had several patients during an artificial pneumothorax refill make expulsory efforts with pressures ranging from +50 to +65 for women and +109 to +249 for men. A much lower value was reached during a laugh or cough—these and subsequent readings are recorded in centimeters of water.

We have not had the temerity to produce a very small pneumothorax to enable us to study the normal intrapleural changes during labor. However, we have had the opportunity of making observations upon artificial pneumothorax during delivery.

Protocols. CASE 1.—Multipara, aged 35. Right lung, 40% collapsed; duration, 1 month. Pulmonary tuberculosis. Delivered, August 28, 1932, at the Rochester General Hospital.

Anesthesia.	Inspiration.	Expiration.	Remarks.
	−14	+ 5.0	Before onset of labor.
Gas oxygen:			
Deep	−16	+ 7.0	Late 2d stage.
Light	−12	+ 4.0	
Deep	−16	+ 7.0	Head presenting.
Deep	..	+83.2	Head presenting during pain.
Deep	..	+85.8	Birth of head.
Deep	+52	+57.0	Expulsion of placenta.
None	+ 4	+11.0	
	− 9	+ 2.0	After 250 cc. refill given.

CASE 2.—Primipara, aged 22. Right phrenectomy, November 11, 1927. Artificial pneumothorax, 75% collapse; duration, 5 years. Bronchiectasis of right middle lobe. Delivered, August 18, 1933, at the Rochester General Hospital.

Anesthesia.	Inspiration.	Expiration.	Remarks.
	−5	− 2	Beginning of refill.
	+8	+13	After 125 to 200 cc. air.
	−1	+ 4	End refill during 2d month pregnancy; mediastinum displaced.
	−3	+ 2	End refill 4th month pregnancy; mediastinum displaced.
Gas oxygen:			
Deep	−5	+ 4	Head presenting.
Deep	−6	+31	Head delivered.

Needle slipped out—no further readings.
Voluntary experiment +50, +65.

Pressure since delivery has been further reduced to $+1\frac{1}{2}$ on account of movable mediastinum.

At the time of delivery the needle was inserted during a pain at

the same location used for a refill 2 weeks previously, but the diaphragm had risen further and the needle had to be reinserted an interspace higher to enter the pleura. Since delivery the same location is used as before for refills, the diaphragm having returned to its previous level.

CASE 3.—Primipara, aged 28. Left lung, 85% collapse; duration, 5 years. Pulmonary tuberculosis. Delivered, September 19, 1933, at the Genesee Hospital.

Anesthesia.	Inspiration.	Expiration.	Remarks.
	−20	− 8	Refill, average before onset of labor.
	− 5	− 2	End 600 to 800 cc. air.
None	−10	0	Between pains.
None	−13	− 3	Between pains.
None	+10	+26	During pain.
	+20	+35	During pain.
Gas oxygen:			
Deep	+27	+45	During episiotomy.
Deep	+24	+40	Head delivered.
None	− 8	+ 1	After delivery.
None	−11	+ 7	500 cc. refill.

CASE 4.—Multipara, aged 22. Left lung, 60% collapse; duration, 2 years. Pulmonary tuberculosis. Delivered by Cesarean section, October 31, 1933, at Strong Memorial Hospital.

Anesthesia.	Inspiration.	Expiration.	Remarks.
	− 2	+2	End last refill 400 cc.
	− 3	$-1\frac{1}{2}$	Before operation begun.
Local	−11	0	During injection of skin.
	−14	−8	
Gas oxygen:			
Light	− 7	+5	
Deeper	− 9	+3	Cutting skin.
Deep	− 6	+4	Cutting peritoneum.
Deep	− 4	+6	Cutting uterus.
Deep	− 6	+4	Stitching uterus.
Light	− 4	+1	Stitching skin.
Discontinued	− 3	+2	End 75 cc. refill.

Comment. It would seem that as each of these patients was under deep gas-oxygen anesthesia and rebreathing approximately 2 to 5% CO_2 during the actual delivery, the intrapleural pressure readings are probably lower than would obtain in delivery without anesthesia.

The change in the rigidity of the mediastinum in Case 2, beginning at the 2d month of pregnancy, is puzzling. Prior to this time a rather high pressure was used to maintain collapse of the bronchiectatic middle lobe. If lower pressure was used, cough and expectoration returned, but with a well-maintained collapse none occurred, in spite of the fact that opaque oil injected into the collapsed lobe showed the bronchiectatic area still open and of almost the same size as before the treatment was begun. Since delivery the mediastinum remains less rigid and the intrapleural pressure has been still further lowered at refills.

Case 1 had by far the smallest pneumothorax and showed the highest pressure reading during labor. Case 3 had the largest pneumothorax, but showed higher readings than Case 2. However, in Case 2 the readings may have been affected by the fact that the mediastinum showed queer behavior and the diaphragm was fixed by a previous phrenectomy. In addition, Case 2 was the most frail of all the 3 normal deliveries.

While 4 cases constitute a very small number from which to draw deductions, nevertheless these observations suggest to us certain conclusions:

1. Is not delivery by Cesarean section preferable to spontaneous delivery in the presence of serious cardiac or pulmonary disease?
2. Is not the increased intrathoracic pressure during labor most probably accompanied by lowered pressure with increased blood and lymph flow following pains and after delivery? This, if true, would partially account for an exacerbation of a latent pulmonary tuberculosis or spread of an active process.
3. Might not the frequent and extreme intrathoracic pressure changes so traumatize the pulmonary scar tissue as to permit a reactivation or spread of tuberculosis?
4. Does not the increase in intrathoracic pressure with the consequent change in the circulation during violent exertion account for some sudden deaths in heart disease?

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BOOK REVIEWS AND NOTICES

THE AUTONOMIC NERVOUS SYSTEM. By ALBERT KUNTZ, PH.D., M.D., Professor of Micro-Anatomy in St. Louis University School of Medicine. Pp. 697; 73 illustrations. Second edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, $7.50.

FEW parts of the body have been as much neglected in the average medical curriculum as the autonomic nervous system. It is a healthy sign, then, that this important work should require a new edition in the short space of 4 years. For the present edition, which combines even more than the first the anatomic, physiologic, pathologic and clinical aspects, the high praise of our former review (AM. J. MED. SCI., **179**, 842, 1930) can only be emphasized. "No student or physician can afford to do without it." E. K.

RULES FOR RECOVERY FROM PULMONARY TUBERCULOSIS. A Layman's Handbook of Treatment. By LAWRASON BROWN, M.D., Saranac Lake, N. Y. Pp. 275. Sixth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, $1.75.

THE steady demand for this little book, from both patient and physician, has made it a recognized piece of equipment, to be kept in repair and modernized like any other device in the campaign against tuberculosis. Dr. Brown has given Education parity with Rest, Good Food and Fresh Air in this campaign, and brought the subject up to date. The sixth edition has all the merit of previous editions and includes new chapters on the surgical treatment of tuberculosis and convalescence. These chapters, from this authoritative hand, will serve to answer the many questions arising in patients' minds on the new forms of treatment. E. L.

INTERNAL MEDICINE. Its Theory and Practice. Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P., Professor of Medicine in the Tulane University of Louisiana School of Medicine; Senior Visiting Physician to the Charity Hospital, New Orleans. Pp. 1288; 35 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1934. Price, $10.00.

IN his review of the first edition the Reviewer ventured to predict that this volume would take its place as a standard text in American literature. The appearance of a second edition within less than 2 years of the first seems amply to confirm this view. There are twenty-six contributors, all holding professorial appointments in medical schools. The subject matter has been thoroughly revised and new material has been added, including diseases of the lymphatic vessels, tuberculosis of the kidneys and urinary tract, a section on the classification of arthropods involved in disease transmission, and additional material on bacillary dysentery. Dr. Musser is to be congratulated on the excellence of his text-book. R. K.

CATARACT. ITS ETIOLOGY AND TREATMENT. By CLYDE A. CLAPP, M.D., F.A.C.S., Associate Professor of Ophthalmology, Johns Hopkins University; Professor of Ophthalmology, University of Maryland, etc. Pp. 254; 92 illustrations. Philadelphia: Lea & Febiger, 1934. Price, $4.00.

THIS excellent text covers much more than its title indicates. It is not only a review of our knowledge of the various forms of cataract but includes also other pathologic conditions of the lens, such as the congenital anomalies and dislocation. Following two chapters on the development and comparative anatomy of the lens, by Ida Mann, are chapters on the anatomy, physiology and chemistry of the normal and pathologic lens. The various theories of the pathogenesis of cataract are discussed and the various methods for the removal of cataracts are adequately presented. It is a highly commendable monograph. F. A.

HUMAN STERILITY. Causation, Diagnosis and Treatment. By SAMUEL RAYNOR MEAKER, M.D., Professor of Gynecology, Boston University School of Medicine; Gynecologist, Massachusett Memorial Hospitals, etc. Pp. 276; 27 illustrations. Baltimore: The Williams & Wilkins Company, 1934. Price, $4.00.

THIS manual is one of a series of publications sponsored by the National Committee on Maternal Health. The author offers as his apologia the need for assembling the established facts on the subject, as well as to offer a manual of clinical procedure based upon a large series of cases studied by the group method. In the study group a gynecologist, a urologist, an endocrinologic diagnostician and an internist were included. The collaborators have contributed special chapters relating to their particular fields. Beginning with the nine normal standards of absolute fertility the authors reverse them in the causative factors of infertility and upon this basis the text is developed in an exhaustive discussion of both the male and female factors.

The incidence and distribution of causative factors in a series of 100 infertile couples are tabulated. It is interesting to note that pituitary dysfunction ranked highest in both male and female constitutional factors, 33 and 26 respectively, and that thyroid conditions accounted for 21 factors in the male but only 6 in the female, while protein starvation, which the author, in discussing diet, states is the most marked dietary fault, accounted for 13 factors in the male and 20 in the female.

In addition to the history and physical examination the galactose tolerance test was used to determine pituitary disease. In the local factors, chronic prostatovesiculitis (18 cases) was most frequent in the male; while hypoplasia (42 cases), tubal occlusion (38 cases) and viscosity of endocervical secretions (31 cases) were the most frequent findings in the female.

The various procedures used, the technique, the results, the interpretations of the findings and the treatment of abnormal conditions is exceptionally well presented. The working schedule of the group practice is fully presented with sample charts. The concluding chapter deals with the prevention of involuntary sterility. This manual is a very thorough presentation of the subject and will be of undoubted value to those working in this field. P. W.

HYGIENE FOR FRESHMEN. By ALFRED WORCESTER, A.M., M.D., SC.D., Henry K. Oliver Professor of Hygiene, Harvard University. Pp. 151. Springfield, Ill.: Charles C Thomas, 1934. Price, $1.50.

THERE has been a great need for a hygiene textbook that is concise and yet accurately and clearly covers the fundamentals that should be

taught college freshmen. The author seems to have met these requirements fairly well in this short, inexpensive book. The introduction interestingly points out the importance of a knowledge of hygiene for college men. The chapters cover Biology, Circulation, Glands, Nutrition, Digestion, Muscles, Nerves, Mental Hygiene, Reproduction, Disease Prevention and Immunity. The index is complete, but the glossary is rather short, listing only 28 words. There are no illustrations nor is there a list of books for collateral or advanced reading, which appear especially necessary for most elementary texts. On the whole the book is well written and covers the subject as thoroughly as possible in so short a course. It is recommended as a textbook for college freshmen taking a hygiene course consisting of a weekly lecture for one-half year. N. B.

LINCOLN'S NEW SALEM. By BENJAMIN P. THOMAS. Pp. 128; illustrated. Springfield, Ill.: The Abraham Lincoln Association, 1934. Price, $1.00.

ASIDE from the interest attaching to this picture of the early stages of Lincoln's gradual development and the important favorable influence that New Salem had in shaping our "greatest American," this little book has a special message to medical men in portraying the village's two doctors and the characteristic medical practice in a pioneer community of our Middle West. In 1831, the month before Lincoln came to New Salem as a flatboat hand, arrived John Allen, a graduate of Dartmouth Medical School, only two years after the town had been planned and laid out. The next year came Francis Regnier who, with Dr. Allen, figured prominently in the intellectual life of the community (see illustrations of their log cabin living rooms and offices). Malaria, typhoid and smallpox were endemic with not infrequent epidemics of cholera. As usual they "purged, bled, blistered, puked and salivated," but faith doctoring and primitive magic doubtless had a more numerous following. In the town reconstruction that is now fortunately progressing, the two doctors' houses have already been included. E. K.

CLINICAL TOXICOLOGY. Modern Methods in the Diagnosis and Treatment of Poisoning. By ERICH LESCHKE, Professor of Internal Medicine in the University of Berlin. Translated by C. P. STEWART, M.Sc., PH.D., Lecturer in General Biochemistry, University of Edinburgh; Senior Biochemist, Edinburgh Royal Infirmary; and O. DORRER, PH.D., Research Assistant to Professor Wieland, Munich. Pp. 346; 25 illustrations. Baltimore: William Wood & Co., 1934. Price, $5.

THIS compact statement by a well-known German clinician was written for the practising physician from the physician's standpoint. It is thus an adjunct to, not an inadequate rival of, the larger text-books written by pharmacologists. With the increasing frequency of industrial poisoning and suicide, the book is of timely interest and value. E. K.

JÖNS JACOB BERZELIUS. Autobiographical Notes Published by The Royal Swedish Academy of Sciences. Through H. C. SÖDERBAUM. Translated from the Swedish by OLOF LARSELL, Professor of Anatomy, University of Oregon Medical School, Portland. Pp. 194; illustrated. Baltimore: The Williams & Wilkins Company, 1934. Price, $2.50.

IF medical readers require special inducement for reading this interesting autobiography of one of the greatest of 19th century chemists, it can be

supplied from consideration of his many medical contacts. First, a student of medicine and chemistry under Afzelius, he was later assistant physician at the Spa Medevi, where he published his first work on an analysis of these waters. Soon after receiving the M.D. degree, he was made adjunct and later full professor of medicine and pharmacy at Stockholm, where he was one of the founders of the Swedish Medical Society.

In these diary-like notes, now first translated into English, one will learn less about his numerous and important achievements than about the circumstances of his daily existence and the backgrounds of his period. His chemical discoveries are easily ascertained elsewhere, but here only we can learn of his minor achievements and vexations, his quarrels with Davy and Young, his honors and his failures, all told in a pleasantly naive style that has been retained by the translator. The book is a worthy successor to the preceding publications by this Society. E. K.

PARASITISM AND DISEASE. By THEOBALD SMITH, Director Emeritus of the Department of Animal Pathology, Rockefeller Institute for Medical Research. Pp. 196. Princeton, N. J.: Princeton University Press, 1934, on the Louis Clark Vanuxem Foundation. Price, $2.00.

THIS book is developed about the principle that "parasitism may be regarded, not as a pathological manifestation, but as a normal condition having its roots in the interdependence of all living organisms." The many diverse relations between host and parasite are harmonized by the hypothesis that, for both parasite and host, two factors, one of offense and one of defense, operate to maintain equilibrium. It is indeed fortunate that one who has been so intimately and richly associated with the development of parasitology has given us this discussion of the biology of parasitism.

H. R.

ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY, VOLUME X, MONOGRAPH XVI, PART II, INFLUENZA. By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), Hon. Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London, and ROBERT THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 916; illustrated. Baltimore: The Williams & Wilkins Company, 1934. Price, $17.50.

PART I of this monograph deal exhaustively with the part played by the various bacteria found in influenza; Part II takes up in a systematic and thorough manner the Complications and Sequelæ, Bacteriology of Influenzal Pneumonia and its Pathology. There are chapters on the Epidemiology and Modes of Possible Transmission, and 150 pages on Prophylaxis, Preventive Measures and Treatment.

In their own summary the authors state, "From the mass of evidence upon the subject it must now be assumed that Pfeiffer's bacillus *per se* is not the prime infective agent in influenza" (p. 1358). From a study of the work of Smith, Andrews and Laidlaw (Lancet, **2**, 66, 1933), they feel that "as this work appears to have been most carefully controlled, the results are strongly conclusive that a virus is the primary cause of influenza." The virus appears "to act primarily as an intensely toxic irritant, producing a profound toxemia" and "hyaline necrosis of the terminal bronchiolar and alveolar walls, causing a rapid and profuse outpouring of serum and red blood cells in numerous patchy areas throughout the lungs" (pp. 1077 and 1366).

Sodium ricinoleate, as a preventive measure and for the local treatment of nasal colds and influenza in the earliest stages, was found to be the most efficacious remedy tried (p. 1261). The authors state that "vaccines are of value in the treatment of the respiratory complications of influenza and that successful results have been recorded not only in prevention, but in the treatment of influenzal pneumonia" (p. 1229). "The employment of convalescent influenza serum in the serum prevention of influenza certainly deserves a trial" (p. 1372) and although the results of such treatment in influenzal pneumonia are at variance, "there is evidence to indicate that this method if used early and given in sufficiently large amounts would appear to have a specific effect" (p. 1239).

The monograph contains 4500 references to foreign and American literature from which whole pages of verbatim quotations are transposed. While repeated reference to the same report at times becomes monotonous this is more than compensated for by the wealth of material it contains. The general format of the monograph maintains the excellence of the previous volumes, but it is regrettable that no photographs of the pathology of influenza were included. J. C.

BENJAMIN RUSH. Physician and Citizen (1746–1813). By NATHAN G. GOODMAN. Pp. 421; illustrated. Philadelphia: University of Pennsylvania Press, 1934. Price, $4.00.

THAT such an important, versatile and interesting figure as Benjamin Rush should have waited 121 years for his biography is indeed strange; that it should eventually have been so efficiently set down is a matter for general satisfaction. The author's four years of study on an unusually rich source of material, especially at the Library Company's Ridgway branch (founded by Rush's son, James) has produced not only a scholarly, authoritative, well documented biography of "an important figure in our nation's past," but also an interesting narrative adequately enriched with sidelights from one of the most colorful periods of our history.

Very properly more than half the book is devoted to Rush's medical career, for "it is upon his fame as a physician that Rush's immortality will rest." Description of his 5 year, mutually satisfactory apprenticeship with Redman, attendance at Shippen's anatomy lectures (the seed that developed into the country's first medical school), his graduation at Edinburgh, studies in London and Paris, and subsequent successful practice in Philadelphia introduces the reader to a remarkably intelligent discussion of Rush's Cullenian theories of disease, of his heroic behavior in the yellow fever epidemics and of his reasons for his plan of excessive purging and bleeding. One misses—on first reading at least—the Sampson anecdote, his pet name for his favored drug calomel, because, so his detractors said, it had killed its thousands. Likewise one misses Holmes' tart completion of Rush's avowal that while medicine had been his wife, Science had been his mistress. Holmes, it will be remembered, allowed that it would have been better for all concerned if he had devoted more of his time to the legitimate object of his affections! Nevertheless, his contributions to medical science were considerable: while his chance observation that mosquitoes were more numerous in yellow fever years deserves little praise, the opposite is true of his original description of dengue, of his masterly observations on the nature and treatment of mental diseases, and of his correlation of distant disease with focal infection of the teeth. The importance of this latter concept has only been recognized within recent years. Rush's account of the 1793 epidemic of yellow fever won him international fame. After nearly a half century of intense activity, during which time he taught more than

3000 students, Rush was generally recognized as the leading medical authority and teacher of the country, "the Sydenham of America."

To many the account of his non-medical activities may be of greater interest. A philanthropist, whose actions followed close on the heels of thought, Rush early became a defendant of colonial rights. Inspirer of Thomas Paine's important pamphlet, "Common Sense," writer of many himself, Member of the Continental Congress, Signer of the Declaration (the only Doctor of Medicine but not the only physician who signed), Rush's position as a patriot is ensured. His medical services in the Revolution were also important, though from his bitter quarrel with Shippen, the Director General, he emerged unsuccessfully and at least not without blame. In this, as in the much discussed quarrel with Washington, Goodman believes that Rush, though impulsive and tactless, was inspired by good motives, and had much evidence to support his stand. Though elsewhere outspoken in criticisms of Washington, he foolishly (not cowardly) stooped to anonymity in a personal attack. Though a friend of Mifflin and Conway, there is no evidence, in Goodman's opinion, to show that Rush was implicated in the Conway Cabal. Non-controversial were Rush's activities toward freeing the negro, abolishing the death penalty and restricting the abuse of alcohol and tobacco. Founder of the first free dispensary, of Dickinson College, and one of the founders of our College of Physicians, a man of intense feeling and prompt action, Rush offers a splendid though difficult opportunity to the biographer. That Dr. Goodman has performed his task ably will be apparent to the reader. The University of Pennsylvania Press, too, is to be congratulated on sponsoring this work which deserves widespread popularity. E. K.

THE COMPLEAT PEDIATRICIAN. Practical, Diagnostic, Therapeutic and Preventive Pediatrics. By WILBURT C. DAVISON, M.A., D.Sc., M.D., Professor of Pediatrics, Duke University School of Medicine, and Pediatrician, Duke Hospital. Unpaged. Durham, N. C.: Duke University Press, 1934. Price, $3.75.

NOT long since, the scientific world was jostled and then mildly amused at suggestions for the replacement of scientific journal articles by minute scrolls, kept in a central office, which could be sent out on demand and read under a magnifying glass. Similar thoughts are suggested by the fine print and modernistic condensations of the "Compleat Pediatrician." From a pleasantly pseudoantique title page, one passes through a conventional preface to a complexity of type changes, cross-reference numbers, symbols and abbreviations that demand a fortitude that many readers will not produce. However, once the method is comprehended and sufficiently practised, one suspects that the author's hope has been accomplished, namely, to produce a complete "ready reminder" of pediatric symptoms and signs, with alphabetically arranged diseases (diagnosis and treatment) sufficiently small "to be carried, like a stethoscope, in a physician's pocket or bag." (For suggested contents of said bag, see Appendix C.) E. K.

SEX-HYGIENE. What to Teach and How to Teach It. By ALFRED WORCESTER, A.M., M.D., Sc.D., Henry K. Oliver Professor of Hygiene, Harvard University. Pp. 134. Springfield, Ill.: Charles C Thomas, 1934. Price, $2.50.

THE proper teaching of sex-hygiene is a difficult problem. Most books discuss the anatomy and physiology of the sexual apparatus and elaborate on the venereal diseases, stressing their frequency and horrible consequences.

Many teachers agree that this is not the best method of approaching the subject; that the sex urge is too great to be overcome by mere fear of the venereal diseases. This is well borne out by the morality of many medical students and doctors, who, above all others, should be well acquainted with the medical aspect of sex. There remains only one course to pursue: an attempt to educate character by appealing to the morals of the individual.

Doctor Worcester has shown us an admirable way of handling sex problems of his concept of "the physiological basis for sexual morality as our trusteeship of the germ plasm." We are also made to see that the so-called sex urge is really a "parental urge and is the underlying motive in all that is loveliest in our lives." These principles, together with a gentle reminder of the doctrine of the great kinship of all mankind, constitute the substance of the text. The book consists of a collection of addresses delivered by the author before medical, religious and lay groups of both sexes. There is very little mention of the anatomy and physiology of the reproductive system and the usual somewhat morbid anatomic drawings are fortunately lacking. The venereal diseases and abnormal sex habits are sufficiently covered. The book contains much of value not only for the patient and student but for the physician and nurse as well. It is one of the best presentations of sex-hygiene that has been seen for some time and is well worth recommending. N. B.

Applied Anatomy. By Gwilym G. Davis, M.D., Late Professor of Orthopedic Surgery and Associate Professor of Applied Anatomy in the University of Pennsylvania. Pp. 717; 674 illustrations. Ninth Edition reset, reillustrated and completely revised by George P. Muller, M.D., Professor of Clinical Surgery, Graduate School of Medicine, University of Pennsylvania; Surgeon to the Misericordia and Lankenau Hospitals. Assisted by Drs. B. J. Alpers, R. A. Kimbrough, Jr., S. W. Moorhead, I. S. Ravdin and S. D. Weeder. Philadelphia: J. B. Lippincott Company, 1934. Price, $9.00.

The appearance of a ninth edition of this work is a real testimony of its merit. The book has been reset, and completely revised by Dr. Muller, assisted in the chapters on neurology by Dr. Alpers, on gynecology by Dr. Kimbrough, on urology by Dr. Moorhead, on the abdomen by Dr. Ravdin and in those on the extremities by Dr. Weeder. It has largely retained its previous form, discussing the regional anatomy and pointing out the applications of anatomical facts in surgical procedures. The excellent illustrations by E. F. Faber are scattered profusely throughout the book. The text has been brought up to date in practically every particular, although the Reviewer looked in vain for some discussion of the sympathetic nervous system, which has risen to considerable prominence in the past few years. This reliable guide to regional anatomy should find a prominent place in the libraries of all surgeons. L. F.

Studies in Blood Formation. By T. D. Power, M.D., M.R.C.P., D.P.H., D.P.M., Deputy Medical Superintendent, Brentwood Mental Hospital. Pp. 124; 25 illustrations. London: J. & A. Churchill, Ltd., 1934. Price, 8s. 6d.

The author, primarily concerned with the study of insanity, began these investigations in order to elucidate mechanisms that have been used in the treatment of the insane. They are to be commended as carefully planned and executed and well controlled. Some statements or deductions to which one takes exception may pardonably be ascribed to a presumably short acquaintance with hematology. Thus the description of the Schilling

method is far from adequate; the deductions (probably incorrect) about amitotic budding and that granulocytes in the artificially produced leukocytoses do not go through the myeloblast stage fail to take into account the limitations of the fixed tissue method; and so on. Such important matters as the need for repeated rather than single counts, and for taking bone marrow specimens at several levels, on the other hand, get timely emphasis. Especially interesting are the demonstrations that sulfosin leukocytosis is due to newly formed cells; that thyroxin stimulates erythropoiesis and hastens differentiation and that therapeutic malaria produces a macrocytic anemia, both hemolytic and aplastic in type. E. K.

THE DOCTOR IN HISTORY. By HOWARD W. HAGGARD, Associate Professor of Applied Physiology in Yale University. Pp. 408; illustrated. New Haven: Yale University Press, 1934. Price, $3.75.

WITH the increasing interest of the general public in the behavior of their bodies in health and disease, there has lately arisen a considerable group of books on various popularized aspects of medicine, of which the author's Devils, Drugs and Doctors is a prominent example. The present book tells in the same vivid, entertaining manner the story of medicine as seen through the lives and achievements of some of its principal exponents. From the anonymous Cro-Magnon witch doctor depicted in his ceremonial dress down through the ages to Gorgas of Panama Canal fame, the story unrolls with a compelling interest and yet without the inaccuracy that one often finds in such works. The illustrations are, especially for a University Press, poorly reproduced; their subjects and arrangement, too, are below the average that the book maintains. Especially interesting are the chapters of historical importance, such as those on the Black Death and the Mental Contagions. For many more than the author's children, for whom the book was written, should this "history of health" afford entertaining instruction. E. K.

NEW BOOKS.

Amebiasis and Amebic Dysentery. By CHARLES F. CRAIG, M.D., M.A. (HON. YALE), F.A.C.P., F.A.C.S., Colonel, United States Army, Retired, D.S.M., Professor of Tropical Medicine and Head of the Department of Tropical Medicine, School of Medicine, Tulane University of Louisiana, New Orleans, etc. Pp. 315; 54 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, $5.00.

Manual of Clinical Laboratory Methods. By PAULINE S. DIMMITT, PH.G., Medical Technologist for the Stout Clinic, Sherman, Texas, etc. Pp. 156; 36 illustrations, including 7 colored plates. Philadelphia: F. A. Davis Company, 1934. Price, $2.00.

American Medicine. By DR. HENRY E. SIGERIST, The William H. Welch Professor of the History of Medicine, The Johns Hopkins University. Translated by HILDEGARD NAGEL. Pp. 316; illustrated. New York: W. W. Norton & Co., Inc., 1934. Price, $4.00.

The Heart Visible. A Clinical Study in Cardiovascular Roentgenology in Health and Disease. By J. POLEVSKI, M.D., Attending Physician and Cardiologist, Newark Beth Israel Hospital. Pp. 207; 122 illustrations. Philadelphia: F. A. Davis Company, 1934. Price, $5.00.

Hormone und innere Sekretion. (Band 19 of Wissenschaftliche Forschungsberichte, Naturwissenschaftliche Reihe, Herausgegeben von Dr. Raphael Ed. Liesegang, Frankfurt a. M.) By DR. FRITZ LAQUER, Wuppertal-Elberfeld, Professor an der Universität Frankfurt. Pp. 368. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 18.

To Remind—A Biological Essay. (The Abraham Flexner Lectures, Series No. 2.) By SIR WILLIAM BATE HARDY, M.A. (CANTAB.), F.R.S., HON. D.SC. (OXON.), HON. LL.D. (ABERDEEN, EDINBURGH, BIRMINGHAM), Fellow of Gouville and Caius College; Director of Food Investigation, Department of Scientific Industrial Research, etc. Pp. 45. Baltimore: The Williams & Wilkins Company, 1934, for Vanderbilt University. Price, $1.00.

The Farm Chemurgic. By WILLIAM J. HALE, PH.D., Research Consultant, The Dow Chemical Company. Pp. 201; 5 figures. Boston: The Stratford Company, 1934. (No price given.)

Heredity and Disease. By OTTO L. MOHR, M.D., Professor of Medicine, The Royal Frederiks University, Oslo. Pp. 253; 107 illustrations. New York: W. W. Norton & Co., Inc., 1934. Price, $3.50.

Verhandlungen der deutschen Gesellschaft für Kreislaufforschung. Seventh Session. By PROFESSOR DR. EB. KOCH, Bad Nauheim. Pp. 326; 65 illustrations. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 15.

The Principles of Therapeutics. (The Abraham Flexner Lectures, Series No. 3.) By FRANCIS RICHARD FRASER, M.A. (CANTAB.), M.D. (EDIN.), F.R.C.P. (LOND.), Professor of Medicine in the University of London. Pp. 135. Baltimore: The Williams & Wilkins Company, 1934, for Vanderbilt University. Price, $2.00.

Erbpathologie, Ein Lehrbuch für Ärzte. (Band 18 of Medizinische Praxis, Sammlung für ärztliche Fortbildung. Herausgegeben von Prof. Dr. L. R. Grote, Prof. Dr. A. Fromme, Prof. Dr. K. Warnekros.) By Dr. O. FREIHERR VON VERSCHUER, Ausserordentlicher Professor der Universität Berlin und Abteilungsleiter am Kaiser-Wilhelm-Institut für Anthropologie, menschliche Erblehre und Eugenik, Berlin-Dahlem. Pp. 213; 32 illustrations. Leipzig: Theodor Steinkopff, 1934. Price, Rm. 8.

Clinical Pathology of the Jaws. By KURT H. THOMA, D.M.D., Charles A. Brackett Professor of Oral Pathology in Harvard University; Oral Surgeon to the Brooks Hospital, etc. Pp. 643; 423 illustrations. Springfield, Ill.: Charles C Thomas, 1934. Price, $9.00.

Mental Health. Past, Present, and Future. (The Colver Lectures, 1932.) By ARTHUR HILER RUGGLES, M.D., Superintendent of Butler Hospital, Providence, R. I. Pp. 104. Baltimore: The Williams & Wilkins Company, 1934, for Brown University, Providence, R. I. Price, $1.50.

Benign, Encapsulated Tumors in the Lateral Ventricles of the Brain. Diagnosis and Treatment. By WALTER E. DANDY, M.D., Adjunct Professor of Surgery, Johns Hopkins University. Pp. 189; 83 illustrations, 2 tables. Baltimore: The Williams & Wilkins Company, 1934. Price, $4.50.

Tumors of the Female Pelvic Organs. By JOE VINCENT MEIGS, A.B., M.D., F.A.C.S., Instructor in Surgery, Harvard Medical School; Surgeon to Out-Patients, Massachusetts General Hospital, etc. With a Foreword by ROBERT B. GREENOUGH, M.D., President-Elect of the American College of Surgeons, 1933–1934, etc. Pp. 533; 261 illustrations, some in colors, and 49 tables. New York: The Macmillan Company, 1934. Price, $6.00.

Fifty Years of Medicine and Surgery. An Autobiographical Sketch. By DR. FRANKLIN H. MARTIN. Forewords by WILLIAM J. MAYO, M.D., Rochester, Minn., and GEORGE W. CRILE, Cleveland, Ohio. Pp. 449; illustrated. Chicago: Surgical Publishing Company, 1934. (Price not given.)

Diättherapie der Lungentuberkulose. By DR. MAX GERSON, Wien. Mit Röntgenbefunden und einem Röntgenkapitel von DOZENT DR. FELIX FLEISCHNER, Wien. Pp. 619; 154 illustrations. Leipzig: Franz Deuticke, 1934. Price, M. 36.

NEW EDITIONS.

The Science and Practice of Surgery. By W. H. G. ROMANIS, M.A., M.B., M.CH. (CANTAB.), F.R.C.S. (ENG.), F.R.S. (EDIN.), Surgeon and Lecturer on Surgery, St. Thomas's Hospital, etc., and PHILIP H. MITCHINER, M.D., M.S. (LOND.), F.R.C.S. (ENG.), Honorary Surgeon to H. M. the King; Hunterian Professor, Royal College of Surgeons of England, etc. Pp. 1901; 758 illustrations. Fifth edition, Vol. 1, General Surgery; Vol. 2, Regional Surgery. Philadelphia: Lea & Febiger, 1934. Price, $13.00.

Any text which can rapidly pass through five editions contains real merit. The present edition has been extensively revised. The treatment of peritonitis, fractures, burns and varicose veins has been brought up-to-date. In several particulars the Reviewer criticized the fourth edition (AM. J. MED. SCI., **186**, 574, 1933) but is happy to state that these matters have been thoroughly revised and corrected. Without doubt this edition will receive a hearty welcome which it justly deserves.
I. R.

Gynecology. By BROOKE M. ANSPACH, Professor of Gynecology, Jefferson Medical College. Pp. 832; 679 illustrations, including 10 in colors. Fifth edition, reillustrated, reset and completely revised by the author with the assistance of PHILIP F. WILLIAMS, M.D., Assistant Professor of Obstetrics, School of Medicine, University of Pennsylvania, and LEWIS C. SCHEFFEY, M.D., Assistant Professor of Gynecology, Jefferson Medical College. Philadelphia: J. B. Lippincott Company, 1934. Price, $9.00.

The present edition has been extensively revised and entirely reset. Many chapters have been rewritten and a section devoted to endocrine disorders has been added. In its present form, this book continues to maintain its place as an outstanding textbook.
F. B.

Recent Advances in Allergy. (Asthma, Hay-Fever, Eczema, Migraine, etc.) By GEORGE W. BRAY, M.B., CH.M. (SYDNEY), M.R.C.P. (LOND.), Physician in charge of Children's Department, Prince of Wales Hospital; Assistant Physician, Princess Elizabeth of York Hospital for Children; Clinical Assistant, Asthma Clinic, Guy's Hospital. With Foreword by ARTHUR F. HURST, M.A., M.D. (OXON.), F.R.C.P., Senior Physician, Guy's Hospital, etc.; Chairman, Medical Advisory Committee, Asthma Research Council of Great Britain. Pp. 503; 106 illustrations, including 4 colored plates. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1934. Price, $5.00.

With 70 additional pages of text and over 700 new references, the new edition of this fine work is highly recommended to students and practitioners as a well-rounded treatise on allergy. Its only disadvantage from an American standpoint is its lack of hay fever plant surveys for this country.
R. K.

Practical Surgery of the Abdominal and Pelvic Regions. By JAMES WILLIAM KENNEDY, M.D., F.A.C.S., Surgeon-in-Chief to the Joseph Price Hospital, Philadelphia; Consulting Surgeon to the Norristown, Coatesville and Chambersburg Hospitals, etc. Pp. 861; 133 illustrations, some in color. Second edition. Philadelphia: F. A. Davis Company, 1934. Price, $7.50.

The present edition reviews the surgical and gynecologic teaching and operative technique of the late Dr. Joseph Price. The author, his pupil, feels that the teaching, often debated as radical, has stood the test of time. Especial emphasis is laid upon widening the indications for vaginal hysterectomy; the principles of this operation are extensively illustrated.
P. W.

Physical Chemistry for Students of Biology and Medicine. By DAVID INGERSOLL HITCHCOCK, PH.D., Associate Professor of Physiology in the Yale University School of Medicine. Pp. 214; 28 illustrations. Second edition (with laboratory directions). Springfield, Ill.: Charles C Thomas, 1934. Price, $2.75.

In the new edition are added laboratory directions for students, as well as several new sections to the text. For review of first edition, see this Journal, **186**, 131, 1933.
M. McC.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

JOHN H. MUSSER, M.D.,
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

RECENT STUDIES ON FAT METABOLISM.

In reviewing the recent contributions to the study of fat metabolism one is impressed by the fact that although our knowledge in this important field remains in a chaotic state there are distinct evidences of a more complete understanding of the complex problem than in the past.

Methods. Improvement and modification of methods have been directed in a large part toward the use of small amounts of blood for analysis. Smith and Kirk[1] have combined and modified the technique of Bloor, Pelkin and Allen, and Stoddard and Drury, so that only 0.5 cc. of whole blood is necessary to determine the fatty acid content. Hot benzene extraction is used and titration is carried out with potassium alcoholate. Kirk, Page and Van Slyke[2] have presented a gasometric method for total lipoids, cholesterol (total and esterified), phosphatids, cephalin and total lipoid N, in which lipoids are extracted by an adaptation of Bloor's alcohol ether technique. For total lipoids alone 0.2 cc. of plasma suffices; for the different fractions 0.3 cc. is necessary. Boyd[3] has assembled a group of micromethods evolved by Bloor and his associates and from these has devised a procedure whereby all lipoids known at present in plasma may be determined on a small amount of blood. He uses the oxidative methods because, since it is impossible to state by which method correct lipoid values are most closely obtained, results by several methods could best be compared if each were based on the same principle. The oxidative procedure was the only one which could be applied to all lipoids known at present to be in blood plasma. Schoenheimer and Sperry[4] have developed a micromethod for free and combined cholesterol in which finger blood can be used. A small amount of serum or whole blood (0.2 cc.) is precipitated with digitonin followed by the application of a color reaction to the precipitate. Amounts of cholesterol from 0.02 to 0.15 mg. may be determined.

Schoenheimer[5] has succeeded in developing a method for the separation of unsaturated sterols from a mixture in which saturated sterols are present in large amounts. The technique makes it possible to

isolate and identify cholesterol from human feces and may open up to a greater extent alimentary and biliary studies in cholesterol.

Discovery of quick, simple and accurate methods of determining lipoidal substances in the blood will give impetus to clinical research in this field. That less cumbersome methods lead to more widespread use is evidenced thus far by the use of Rückert's lipokrit method.[6,7] The principle is the same as that in the Gerber milk-fat method. Simplicity and accuracy are claimed and results have been checked against more elaborate, time-consuming methods. Allen[8] has also described a similar quick fat method for plasma. It is accurate, he says, for comparative studies, but determinations of accuracy are not published. It is fast and simple, no filtrations nor extractions being necessary, and employs an alkali reagent, as used in a modified Babcock procedure. Allen recognizes the necessity for further study to establish the applicability of the method for absolute determinations.

In cholesterol estimations as well, need for speed and accuracy has prompted Kamlet[9] to publish a colorimetric method. It appears to be sufficiently accurate for routine clinical work. The Lieberman-Buchard reaction is employed but no heat extraction is necessary, the extraction being carried out on blood dried on filter paper for 2 hours at room temperature. The widest variation from the Bloor-Sackett method was 9 mg. per 100 cc. and the average difference 3.55 mgm. per 100 cc.

Estimation of variations in the quantity and quality of lipoids in the various blood fractions has added appreciably to our knowledge of fat metabolism. Boyd[10] has introduced a new field in his determinations of the lipoid content of the white blood cells, carried out in normal young women midway between menstrual periods. The lipoid content was four times as great as in normal plasma with marked variation in the percentage composition of the component lipoids. As compared to body tissues the white blood cells contain a relatively large proportion of cholesterol esters, which vary from 0 to 75% of the total. Boyd again brings forward the thought that active cells contain a high percentage of phospholipoid and little or no cholesterol esters, while inactive or degenerating cells possess a low content of phospholipoid and an increasingly high amount of cholesterol esters. His results show that those white cells containing the highest per cent of cholesterol ester had the lowest per cent of phospholipoid, suggesting inert cells. When the cholesterol ester content was low the phospholipoid values were elevated, suggesting increased activity. Judged by these standards these cells were in different stages of functional activity, yet by usual standards all appeared the same.

Alimentary Lipemia. The constancy of blood fat levels and the variations which occur in alimentary lipemia constitute an important chapter in fat metabolism. McEachern and Gilmour[11] have shown wide fluctuations in the 5-hour fasting blood cholesterol curve. They conclude that such variations render haphazard studies of blood cholesterol of doubtful value. In 1928 McClure and Huntsinger[12] found only insignificant changes. The experiences of Bruger and Somach[13] were similar to those of McClure and Huntsinger. Ingestion of food gave no appreciable effect. Bloor,[14] too, has shown that with constant dietary and environmental conditions the plasma lipoid level, postabsorptive,

in dogs was satisfactorily constant for 2 years. However, with the ingestion of urea, blood cholesterol changes occur. The ingestion of water alone gives no variations outside of the normal range,[15] but with ingestion of urea the resulting high blood urea was associated with a diminished cholesterol content. Bruger and Poindexter could not account for these changes on the basis of water fluctuation in the blood and made the assumption that the increment in blood urea modifies the plasma colloid structure so that cholesterol tends to decrease appreciably.

Alimentary lipemia, the rise of blood lipoids following the ingestion of fats, has been used to study the effect of certain drugs and hormones upon fat metabolism, a study which is comparable to the use of the glucose tolerance curve in carbohydrate metabolism.[16] Fat is absorbed from the intestine to the blood and from the blood to the tissues. Rony and Ching point out that the process is more complicated than is the carbohydrate curve, for it includes the rate of digestion of fat, which depends on bile and pancreatic secretion. They believe that with normal digestive organs under standard experimental conditions the rate of fat digestion and absorption is fairly uniform and that with this precaution in mind one may use alimentary lipemia curves as approximate measures of the rate of fat "utilization." Appreciating these difficulties in fat tolerance tests these authors showed in dogs that insulin promotes the passage of ingested fat from the blood stream into the tissues. This effect is independent from the effect of insulin on the blood sugar but does "show that deposition of ingested fat is in some way dependent on carbohydrate metabolism." Interesting in comparison with Rony and Ching's results are those of Sullivan and Cameron,[7] who, using the lipokrit technique, showed that the administration of adrenalin caused a lowering of increasing blood fats in the alimentary lipemia of diabetes. There are then two antagonistic hormones producing similar changes, a question which needs further consideration. Sullivan and Cameron interpret their results as evidence to support the view that adrenalin has a direct regulatory effect on fat metabolism. Raab[17] reports that pituitrin decreases the neutral fat content of the blood, a reaction abolished by paralysis of the centers in the tuber cinereum and by transsection of the spinal cord. He concludes that pituitrin has an action on fat metabolism through a nervous pathway.

Chaikoff and his associates[18] found no typical or uniform responses of blood fatty acids in man by ingestion of a single fat. The atypical response is ascribed partially to previously uncontrolled diet and an insufficient time interval to establish a constant nutritional state. Other factors are important also. The authors contend that "the intestinal factors, as yet poorly understood, account in part, no doubt, for the normal variability in the response of the blood lipoids during the absorption of fat." While Rony and Ching contend, as already noted, that under standardized conditions alimentary lipemia curves serve as an index of the rate of fat utilization, these authors consider the uncertainty of rate of absorption as the fundamental weakness in such interpretations. They emphasize also that the variety of methods as well as the differences in the test meals used make difficult the comparison of results of different observers.

The work of Wilson and Hanner[19] on the character of the fatty acids with widely different dietary fats is extremely interesting. They determined the qualitative changes in the blood fat during alimentary lipemia by determinations of the iodin number on the serum following ingestion of 40% cream (iodin No. 30 to 40) and cod-liver oil (iodin No. 165). Calculations of the iodin number of the increment were between 39 and 60 in those fed the cream, and between 118 and 135 in those fed cod-liver oil. These results are interpreted in this light. After ingestion the neutral fat, resynthetized and present in the blood stream, is "largely or entirely composed of the fatty acids contained in the fat ingestion" and not a changed fat of a quality characteristic of the individual person.

Blood Lipoids in Thyroid Disease. A greater understanding of changes in blood lipoids in relationship to basal metabolism and thyroid disease is evident from recent work. The inverse relationship of blood cholesterol to the metabolism in thyroid disturbances is, of course, well known. In experimental animals[20] thyroxin injections have been shown to affect blood lipoid levels raising them in whole blood determinations 20% to 80%. Liver phospholipoids, however, have been found decreased when the basal metabolic rate is elevated by thyroxin.

That the blood cholesterol is specifically related to thyroid function and is independent of changes in basal metabolism except insofar as the change in basal metabolism is a manifestation of thyroid function, is becoming evident in the recent accumulation of data. In nephrosis,[21] for example, "although the total cholesterol is increased and the basal metabolic rate may be decreased there is no constant relationship between the two nor is there any predictable effect on thyroid therapy." In addition, more than a simple quantitative change in blood cholesterol occurs in cretinism. Besides the increase in cholesterol the ratio of esterified to free cholesterol may be changed and the relative proportions of each reversed. With therapy the normal relationship may again be restored. The same authors suggest that the determination of the free to ester cholesterol may be valuable in following the patient under such treatment.

Further evidence that thyroid function rather than the metabolic rate determines the state of blood cholesterol in thyroid disease, is evident from Hurxthal's[22] report. He states that subtotal thyroidectomy is sometimes followed by hypercholesterolemia without clinical myxedema, that the basal metabolic rate may be low postoperatively in the patient with respect to the blood cholesterol, and Roentgen ray therapy of the gland may produce hypercholesterolemia with or without clinical myxedema. Hurxthal[23] also showed that hypometabolism associated with suprarenal or pituitary insufficiency was not accompanied by hypercholesterolemia. He believes that hypometabolism found in these clinical conditions is not due to thyroid failure because of the absence of hypercholesterolemia. If in obesity a hypercholesterolemia is found, a concealed myxedema should be considered. In three definite conditions of endocrine dysfunction—hypothyroidism, Addison's disease and hypophyseal disease (chromophobe tumor)—the thyroid dysfunction alone raised the blood cholesterol over 200 mg. per 100 cc., strongly suggestive evidence that in other conditions the low metabolism is not due to secondary thyroid atrophy. It is further

evident from this work that changes in cholesterol content of the blood with changes in metabolism may be used as a differential point in diagnosis. Another strong link in the chain of evidence that blood cholesterol is independent of basal metabolic rate *per se* is the work of Cutting and his associates.[24] These investigators studied the changes in blood cholesterol after dinitrophenol medication. They reëmphasize the fact that symptoms of hyperthyroidism may be divided into two groups, those resulting from the metabolic stimulation and those from stimulation of the sympathetic nervous system. The former are induced in dinitrophenol medication but not the latter. The results, too, tend to show that blood cholesterol is not controlled by the metabolic rate but rather by other thyroid secretory actions.

There is then, in cholesterol determinations, concrete evidence of the complexity of thyroid function as well as evidence that metabolism varies in endocrine disorders independently of thyroid function. A diagnostic weapon seems probable in the differentiation of those states associated with abnormal metabolism and a means of confirming those cases of supposed hyperthyroidism with normal metabolism and thyroid dysfunction varying independently of the metabolism.

The Essential Fatty Acids. Efforts to show that the body requires certain essential unsaturated fatty acids corresponding to the essential amino acids have been carried further. Evans and his associates,[25] working on rats, showed that normal reproduction without the essential unsaturated fatty acids is impossible. Their findings are striking. About 20% of the females failed to litter after implantation. Six per cent died during littering and in 95% of the pregnancies prolonged gestational periods resulted, displaying interference with the birth mechanism necessary to expel the young on the expected normal day. When littering took place it occurred with great difficulty. An unnatural chalky appearance of the corpus luteum was observed. Addition to the fat-free diet of the essential unsaturated fatty acids was the only factor which markedly improved the animals. Lactation on the fat-free diet was possible but not highly successful. The same authors[26] showed that the unsaturated and not the saturated fatty acids are the essential ones for rats. They call the essential unsaturated fatty acids vitamin F. Absence of these fatty acids is said to produce sterility in male rats.[27]

Hansen and Burr[28] discovered distinct differences in the serum lipoids of rats fed on fat-free and normal diets. Distinct differences were found in the iodin numbers of the two groups. Results[29] indicated that the serum fatty acids of rats fed on fat-free diets are less unsaturated than those of controls. The skin changes observed in rats suffering from the unsaturated fatty acid deficiency disease suggested to Hansen[30] that infantile eczema might be partially dependent on this type of dietary deficiency. Determination of the serum fatty acid in infantile eczema indicated less unsaturation than in controls. He[31] therefore gave oils rich in unsaturated fatty acids to 14 patients, with good clinical results. In 4 subjects followed with iodin numbers the numbers rose to normal figures parallel with improvement. The common use of crude coal tar in these lesions led the author to determine the effect of such therapy on the iodin number.[32] Results were similar to those with unsaturated fatty acids. The author emphasizes, however, that these reports are preliminary and the changes noted need further confirmation.

A further and distinctly separate attempt to relate lipoid metabolism and eczema is the work of Faber and Roberts.[33] Blood lipoids were determined in patients with eczema and in normal controls. Outstanding differences occurred in the serum cholesterol. One-half of the cases showed a hypercholesterolemia. A few values were very low, so that the results were interpreted as demonstrating an instability in cholesterol metabolism. No differences in phospholipoids were noted.

Blood Lipoids in Diabetes. The lipoid changes in diabetes have continued to hold the interest of many observers. Chaikoff, McGavack and Kaplan[18] determined the postabsorptive blood cholesterol in depancreatized dogs maintained on insulin and diet. They found a reduction in the ester cholesterol of the fasting blood in these animals. Curtis, Sheldon and Eckstein[34] quote Allen in stating that, aside from a good dietary supply of fat, the one prerequisite of diabetic lipemia is active severe glycosuria and hyperglycemia, and that in mild cases, or in severe cases which are controlled, the lipemia is never extreme in spite of high fat intake. Therefore, the diabetic lipemia represents more than a mere excess of fat in metabolism. Allen has never seen marked lipemia without acidosis. The findings of Curtis and his associates substantiate Allen's views that severe diabetes alleviated by treatment shows no extreme grade of lipemia. Unlike Allen, however, they found a parallelism between the degree of lipemia and degree of acidosis. Their results indicate that fat ingestion is unimportant in the lipemia if the fats are burned or stored and they believe that the lipemia is a result of almost total diabetes due to the disease itself or to a severe acidosis. In their case showing xanthomata a relationship between the tumors and the lipemia was apparent, for the xanthomata disappeared as the blood fats were reduced to normal levels.

Bruger and Mosenthal[35] also have attempted to determine the factors which control the plasma cholesterol level in diabetes, experiments which supplement those of the work already mentioned. On the injection of insulin, whereas a definite change occurs in the blood sugar, in cholesterol the value "may rise or fall but usually remains unchanged for several hours."

Man and Peters have added greatly to the understanding of lipemia in diabetes. In experiments in which transudation of fluid was produced, and by comparing the protein and lipoids in the serum and in pathologic exudates, they have shown that capillary walls are impermeable to cholesterol, phospholipoids and compounds of saturated and slightly unsaturated fatty acids, as well as to proteins.[36] With these facts as starting points they studied diabetic acidosis[37] to compare changes in lipemia with variations in the serum protein concentration, "for the double reason that not only are proteins indicative of the course of clinical improvement but also that hemoconcentration should produce marked differences in the plasma lipoids if normal capillaries are, as has been demonstrated, equally impermeable to protein and lipoids." Results bore out this reasoning. In acidosis the lipoid fractions were above normal and returned on recovery to lower levels, following the serum proteins. Concentrations of cholesterol more nearly paralleled the proteins than did the other lipoid fractions while contrary to usually accepted views the concentration of the serum fatty acids and cholesterol were not always related. Although variations in

the concentration of the lipoids of the blood depend largely on the degree of hemoconcentration other factors also may play a part. Hemoconcentration is offered as a possible explanation of the unexpected variations in cholesterol noted by Bruger and Somach.[13]

The relationship of cholesterol to obesity and degenerative diseases has been explored by Bruger and Poindexter.[38] Patients with diabetes, essential hypertension, osteoarthritis and arteriosclerosis were studied. The authors point out that the relationship between these diseases and obesity has been stressed for years; that the degenerative diseases, as contrasted to the inflammatory ones, are usually associated with increased blood cholesterol. Their results show that in 53 obese subjects without degenerative processes the plasma cholesterol was normal. However, in many instances when hypertension, diabetes or arteriosclerosis was associated, the cholesterol values were higher. The obese patients eating a diet high in fat had normal blood cholesterol levels unless the degenerative diseases supervened. They therefore conclude that the development of degenerative diseases in the obese is, as a rule, followed and not preceded by hypercholesterolemia and that the elevated cholesterol in the blood in these degenerative changes is usually to be regarded as a complication and not as an etiologic factor.

Bile Salts in Fat Metabolism. In Wright's[39] important experiments upon the biliary system of dogs, he finds cholesterol in bile in the free state only. He finds no esters of cholesterol in normal dog bile. With Whipple[40] he suggests a liver threshold of elimination of cholesterol. It was found possible to raise the blood cholesterol without a large increase in bile cholesterol and also to increase cholesterol elimination in the bile without change in the blood cholesterol concentration. Whereas the esters make up a large part of blood cholesterol they do not appear in dog bile, so that if the normal liver cell has a threshold for cholesterol it will not pass cholesterol esters. To this phase of the problem the authors offer further study. The factors influencing the appearance of cholesterol in the bile are considered, especially the dependence of the cholesterol of the bile on the circulation of the bile salts. The change wrought in the solubility of cholesterol in bile is not the only action of the bile salts, for the effect of bile salts on the liver cell itself is also important. The bile salts, in this conception, would act directly upon the liver cell, change its state, and permit the passage of cholesterol. The bile salts thus modify body function, the authors believe, not only in their "external sector" but also and probably with more importance in their "internal sector." Calculations show that a 10 kg. dog has in circulation 750 to 1500 mg. of cholesterol from which only a very small amount, 10 to 20 mg., appears in the bile daily. This naturally points to the bile as an outlet for surplus cholesterol. However, since the increase in bile cholesterol is insignificant in dogs on diets rich in cholesterol, and since in liver injury due to chloroform both bile salt and cholesterol elimination are decreased in the bile, the bile cholesterol may also be related to the internal cholesterol metabolism going on in the liver cell. They point out a possible clinical application of these views, in that stasis of bile with high cholesterol values favors precipitation of cholesterol and subsequent formation of gall

stones. Not only would bile salts aid this situation by their cholagogue action but also by holding the cholesterol in solution in the bile.

Hawkins and Wright[41] stress the importance of only one variable, one type of injury, in observing changes in blood cholesterol. Using chloroform to produce such injury these observers showed that chronic derangements in liver function cause changes in plasma cholesterol metabolism. Chloroform by mouth decreased the ester cholesterol-cholesterol ratio, while bile duct obstruction raised the amounts of each but left the ratio unchanged. However, low blood cholesterol with dissociation of the esterified to total cholesterol ratio is not due to parenchymal liver injury only. While in biliary obstruction hypercholesterolemia results, if obstruction alone caused the change the free cholesterol of blood should increase much more than the esters with dissociation of the ratio. Experimentally a normal ratio is maintained. That the hypercholesterolemia in biliary obstruction cannot be due to changes in the liver alone is also evident.

Study of cholesterol-cholesterol ester has been proposed as a test to differentiate obstruction and parenchymatous lesions, for as noted in obstruction, the total cholesterol may be elevated with the ratio the same, while in parenchymatous injury the total cholesterol will decrease and the combined cholesterol drop markedly. While this may be true there are cases, as shown in dogs, where the blood cholesterol does not change. Also if the cholesterol is raised by obstruction, liver damage will cause a prompt fall, producing a weakness in the diagnostic index of cholesterol-cholesterol ester.

The authors, however, emphasize the significance of ratio of esterified to total cholesterol as a criterion of impairment of liver function over any change in total plasma cholesterol. While total cholesterol varies widely, the ratio is more constant even in dietary extremes. When values of the ratio fall below the low normal it is an indication of impairment of the functional capacity of the liver.

The studies of Wright and his associates are of extreme importance in laying the foundation of physiology of cholesterol metabolism upon which may be built knowledge of cholesterol pathology.

Lipoid Changes in the Anemias. The lipoid changes in the anemias have been investigated by Muller and Heath.[42] They point out that disturbances in cholesterol and lecithin metabolism frequently occur in anemia but that views in the literature are conflicting. Some say, for example, "that there is no characteristic difference in the blood lipoids in the different types of anemia and that the level of the blood cholesterol and degree of anemia are directly related—a general reaction to loss of cells and hemoglobin in the circulating blood." Muller and Heath believe from their results that whatever is the underlying cause of disturbed lipoid metabolism, anemia *per se* is not directly related to the level of the cholesterol and lecithin phosphorus in the blood. They have studied the cholesterol and lecithin values in various types of anemia. In pernicious anemia a definite relationship between the stage of the disease and blood lipoid was previously shown by Muller. The cholesterol and often the lecithin phosphorus decreased during a relapse, but as remission started a sudden rise in lipoids occurred with the reticulocyte response. However, in the anemia of chronic blood loss the low values did not vary directly with the reticulocytes in

therapy, nor were any relationships to reticulocytes or concentration of hemoglobin or red blood cells found in idiopathic hypochromic anemia. In acute blood loss, they state, however, that as a rule the reticulocyte outpouring was accompanied by hypercholesterolemia and lecithinemia. In cancer of the stomach the low lipoid level remained regardless of the level of the red blood cells, except where the anemia improved with iron therapy.

The differences in behavior of the lipoids in these various types of anemia have led these authors to the conclusions that the plasma lipoid is not directly related to the concentration of red blood cells or hemoglobin. Even with responses to treatment the reactions vary. In chronic blood loss the increase following therapy starts after the reticulocyte response, while in pernicious anemia the response parallels the reticulocytes. The high values of lipoids in acute hemorrhage are not adequately explained. Since low values occur in more severe anemia the authors discount the claim that a lack of red blood cells or decreased oxidation may cause it. Other explanations offered are a sudden decrease in lipase and in metabolism of the lipoids, a sudden outpouring of fats faster than they can be disposed of or possibly in part through displacement of fat by blood forming tissue (Bloor), and a sudden decrease in proteins with compensation by lipoids to help maintain the colloid osmotic pressure (Fishberg). The lowering of the lipoids in chronic blood loss is also inadequately explained at present. Lipoid exhaustion and the possibility of low values because of increased functional activity of the reticulo-endothelial system are entertained. The possibilities of nutritional effects are dispelled in idiopathic hypochromic anemia by the fact that lipoids remained uninfluenced after the anemia improved markedly on iron and on adequate diet.

Lipemia of Pregnancy. The lipemia associated with pregnancy has been considered by Boyd.[43] He finds it very "similar in nature to the lipemia in diabetes, nephritis, chronic alcoholism and persistent hemorrhage. Neutral fat is first increased and later the phospholipoid and cholesterol follow, the increase of the latter two appearing entirely secondary to the neutral fat increase and probably represents some adjustment in the lipoid balance of the body." The most popular theories of the nature of the lipoid increase are reviewed. An endocrine theory with hormones affecting the blood lipoid levels heads the list. Absorption of products of fetal metabolism, placental toxins, change in blood lipase and many others are mentioned chiefly to emphasize the fact that none has been sufficiently proved. Experimental work on rats is discounted since rats do not display hypercholesterolemia in pregnancy.

Studies in lipoid metabolism in pregnancy, as well as outside pregnancy, must embrace determinations of lipoids in whole blood, plasma, and red blood cells because of changes which may be significant in these three fractions. Boyd has found that the lipemia of pregnancy is due almost entirely to increase in plasma lipoids. Since the red blood cells show only slight change, determinations on whole blood give little indication of where the changes are occurring. The neutral fat shows an increase in the first trimester, the cholesterol and phospholipoid in the second. "At term neutral fat is elevated the most (over 100%); phospholipoid and free cholesterol are elevated about one-fourth. The

ratio of phospholipoid to cholesterol and ester cholesterol to total cholesterol are but slightly altered." Boyd concludes that his results place the lipemia of pregnancy in the class of similar persistent lipemias, as diabetes and experimental anemias. He finds no change in the composition of the fatty acids the iodin numbers in the pregnant women being similar to those in the non-pregnant state.

The cholesterol values in nephritic toxemia and eclampsia are higher than in the non-pregnant woman but not different from normal pregnancy.[44]

Xanthomata. The association of xanthomata with derangements in fat metabolism has continued to interest investigators. Michael and Nicholas[45] in 3 cases of xanthoma multiplex and 5 of xanthelasma showed disturbances of fat metabolism manifested by an abnormal distribution of lipoid constituents of the blood or by the results of fat tolerance tests. Chaikoff *et al.*[18] found increased lipoids in the blood of a case of xanthomatosis. This patient failed to show, as did the one of Wile, Eckstein and Curtis,[46] any disturbance of the capacity of the tissues to take up absorbed lipoids, pointing to the view that the increased blood lipoids are derived from fat having already been stored or by synthesis of fat.

A study[47] of the lipoid content of tissues in a case of Schüller-Christian's disease demonstrates that while reported variations in lipoid content of various organs in this disease are marked, lipoids in tissues showed no marked difference from those of normal individuals except in xanthomatous masses.

Cholesterol in Nephritis. Ashe and Bruger[48] reported the cholesterol content of the blood in patients with nephritis, and with nephritis with uremia to investigate the changes in cholesterol when uremia develops. Their results show that a low blood cholesterol in Bright's disease with uremia foretells death, while a high cholesterol carries a good prognosis for the uremia. These findings were in no way correlated with edema. There was some evidence of a reciprocal relationship between cholesterol and urea, but this relationship was offset at times by various compensatory factors making it difficult to determine such a relationship uniformly. While no definite evidence of a cause for this relationship could be detected the authors believe that the low cholesterol values are probably due to such factors as cachexia and anemia.

Maxwell,[49] in a study of plasma cholesterol in nephritis, reports findings directly at variance with those of Ashe and Bruger. In acute cases they found that the plasma cholesterol appeared to be roughly proportional to the edema. In the chronic types variations were very wide and they were unable to demonstrate any satisfactory relationship with the clinical course of the disease. They state that the plasma cholesterol is of little prognostic significance and that they found slight ground to suggest that "an increase in the plasma cholesterol in the absence of edema is an indication of a probable early termination of the case in uremia."

Lipoid Metabolism in Neuropsychiatric Disorders. Because of the high percentage of lipoids in brain tissues, attempts have been made to correlate the lipoid values of the blood with various mental and nervous diseases. Hopkins[50] has determined the whole blood cholesterol in epilepsy. Ketogenic diets producing a fatty acid acidosis and a rise in blood cholesterol suggest that a fall in blood cholesterol may occur

during the active phases of epilepsy. Hopkins' results show that the whole blood cholesterol in epilepsy appears to be significant in indicating the direction in which physicochemical changes are taking place and that the values are slightly lower in epileptics than in normals with a greater 24-hour variation.

In manic depressive psychosis as well, Slight and Long[51] discovered distinct differences from normal. Iodin numbers were lower in depressed cases, indicating a greater proportion of saturated lipoids than in the normals. The authors also conclude that in certain manic depressive cases a disturbance in lipoid metabolism occurs, as shown by the increased lipoid content of the plasma.

Changes in lipoid metabolism in schizophrenia have been shown by Looney and Childs,[52] who found a slight degree of depression of the cholesterol of the whole blood. They state, however, that "although the blood cholesterol values for a series of schizophrenics is somewhat lower than for normals, in a given patient the values cannot be used as an aid in diagnosis, since variability is so great and range so wide that no single determination can be taken as characteristic."

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PEDIATRICS

UNDER THE CHARGE OF

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THE TREATMENT OF CHOREA.

According to Garrison,[1] "Chorea (dancing mania) was probably the result of physical degeneracy plus fanatical religious enthusiasm, and acquired the name of St. Vitus dance from the processions of dancing patients in the Strassburg epidemic of 1418." Because the first scientific description was given by Sydenham[2] in his "Schedula Monitoria" (1686), the condition is called Sydenham's chorea.

For many years the disease was treated empirically by the use of arsenic in the form of Fowler's solution and by salicylates. The latter were given because rheumatism was so often seen in cases of chorea. Later this association aroused interest, and the occurrence together of chorea and rheumatism was studied first by the clinicians and later by the bacteriologists. During the early phases of these studies there was considerable doubt that the association was more than a frequent coincidence; but with the work of Poynton, Payne and others on the bacteriology of these conditions, the rôle of streptococci in both was demonstrated. It followed that the relationship between chorea and acute rheumatic fever was more than casual.

In 1909 the direct relationship between these two diseases had not been established. Such a great authority as Holt[3] wrote as follows: "With reference to the use of drugs, it is advisable to separate from other cases those in which the connection with rheumatism is very close. In the rheumatic cases, salicylate of soda is often efficient, while the drugs usually employed may be absolutely without effect. In a case recently under observation, arsenic had been continued for 2 weeks

without the slightest improvement, when the patient had an intercurrent attack of subacute rheumatism for which salicylate of soda in full doses was given, with the effect of controlling the choreic symptoms promptly and permanently. In the non-rheumatic cases, arsenic is almost universally admitted to be the most valuable remedy we possess. . . ." Kerley[4] in 1919 said: "By treating every case of chorea as though the disease were rheumatism, my results have been strikingly good. Not only is the child given the salicylates, but he is put on an antirheumatic diet. The tonsils should receive careful attention, and in repeated attacks enucleation should be practiced." This author under the heading of "Supplementary Treatment" described the first form of serologic treatment as originated by Goodman, who reported 30 cases of chorea treated by the autoserum method. After having the child lie in bed for 3 or 4 days or longer without any medication, Goodman withdrew from a vein 45 to 50 cc. of blood and rapidly centrifugalized it. The serum was then pipetted off and kept on ice. A lumbar puncture was performed in the usual manner. The fluid was withdrawn slowly and about 20 cc. of the fluid were collected. The serum was then heated to body temperature and very slowly injected into the spinal canal. He warned that such an injection should take from 10 to 15 minutes, and usually 15 to 18 cc. of the serum were used. The patient should retain the recumbent position for at least 1 hour after the injection. From 1 to 4 injections were given, but the interval was not stated. This rather cumbersome procedure, not devoid of danger, did not attain wide use, although Goodman's report showed results that seemed very satisfactory from the standpoint of cures, improvements and the low incidence of recurrences. Incidentally his standard of classifying his results was based on rather rigid requirements. Under cured, he grouped those cases in which all twitchings ceased within a week. Under markedly improved, he grouped those cases in which there was a cessation of all twitchings within 2 weeks. As slightly improved, he classified those where the twitching disappeared at the end of the third week, and as unimproved, those in whom the twitchings were still present during the fourth week.

Other bacteriologic products have been used but with no uniform success, and as a consequence they have not become popular. Mention will be made later of two more recent bacteriologic preparations for the therapy of chorea. Before considering these let us review the treatment of chorea and add several methods that have been recommended. At first there was Fowler's solution, given in small doses gradually increasing to the point of tolerance if necessary. Later salicylates were used either separately or in conjunction with Fowler's solution. Rest in bed, bromids, luminal and similar drugs were used to decrease nervous excitability and to promote absolute rest. With the definite association of rheumatism and cardiac involvement with chorea the indications for rest became more imperative.

Several methods of treatment will now be enumerated or described without regard to their chronologic position in the development of the therapy of chorea. None of these has gained popularity if the dearth of references in the literature may be taken as a criterion. The two exceptions among the newer methods are the nirvanol and typhoid vaccine methods of producing artificial fever. Gopeman[5] reported a

series of 44 chorea cases in children treated by means of reclining baths at skin temperature for considerable periods of immersion. He said: "The sedative effect, which it is the object of this treatment to produce, was generally manifest after about a week. . . ." All the cases responded well after periods of treatment varying from 8 to 12 weeks in the milder ones, and up to 5 months in the severer cases. A certain number of selected cases was treated in the same ward on more usual lines with various drugs, including nirvanol, at the same time that the hydrotherapy treatment was used. It was observed that these responded more quickly, but relapses were more common. The notes of 50 unselected cases treated on more orthodox lines were examined, and the incidence of relapses was compared with those occurring over 4 years in the presented series. In the former group where drugs were used, there were found to be 8 relapses, a ratio of 1 to 6; while in the present series there were 3 relapses or a ratio of 1 to 13.

Leopold and Rothstein,[6] using a ketogenic diet similar to that used for epilepsy in a series of 12 cases of chorea, noted good results in 9. They found that the period which elapsed before the development of a definitely marked ketosis varied from 3 to 8 days. The period of continued ketosis required for the disappearance of the choreiform manifestations was approximately 9 to 24 days. In 2 cases the authors were forced to discontinue the diet after several days before a definite ketosis was even produced, because of the development of acute endocarditis and pericarditis in 1 case, and the contracting of a severe lobar pneumonia in the other. In 1 case of severe chorea in a stout girl of 11 years, weighing 129 pounds, who had displayed marked symptoms of chorea for 7 months prior to her hospitalization, it was impossible to improve her condition. It was noted that although a definite ketosis was produced within 6 days, and the child was kept on the very low carbohydrate stage of the diet, receiving 10 gm. of carbohydrate per day, the production of a ketosis was not constant. Some days the ketosis would be moderate, whereas on others the tests for acetone and diacetic acid in the urine would be negative. Apparently the ketogenic diet may be used with success in most cases of chorea, according to these authors, except those which have acute respiratory or other infections such as a concurrent pneumonia. In some instances it was found that the high fat was not well tolerated, for nausea and vomiting would occur as signs of a fat intolerance without any clinical symptoms of an acidosis developing. In fact, according to weekly chemical examinations of the blood, no material or clinically significant changes in the blood or CO_2 figures occurred. If this condition were found true in a large series of cases, it would seem to show that the ketosis produced, as evidenced by the presence of acetone and diacetic acid in the urine, is not always accompanied by a clinically significant acidosis, such as might be expected to cause a material change in the carbon dioxid combining-power of the blood. The authors felt that the efficiency of the diet had not been proved sufficiently to warrant risking the possibility of causing gastro-intestinal upset in such cases that may have the complications mentioned before. Consequently in treating these children they recommended rest in bed, the use of sedatives and other symptomatic treatment. Whether the ketosis produced in the treatment of chorea will be of any value in the prevention of cardiac com-

plications, they were unable to say with the data at their disposal from the study of this series of cases. They thought, however, that the actual shortening of the duration of the chorea might diminish the possibility of such complications occurring. That the authors failed to be convinced of the efficiency of this treatment of chorea is suggested by the absence of further reports by them after several years. Doubtless it was used by many others anxious to discover a safe and efficient procedure in the handling of this disease, but no evidence of their experiences appears in the literature. Our own experience with the ketogenic diet in the treatment of severe cases was that improvement followed usually only after long periods extending to from 4 to 10 weeks. In some cases the maintaining of ketosis as evidenced by acetone and diacetic acid in the urine was difficult. Another disadvantage that this method has in common with most of the procedures so far recommended in the treatment of chorea is the necessity of hospitalization.

Speaking of the medicinal treatment of chorea, Mutsch[7] says that calcium acetylsalicylic acid or calcium aspirin possesses the means of dealing simultaneously with the three etiologic factors of chorea: rheumatism, nervous strain and calcium deficiency. This was the only mention of calcium deficiency as one of the etiologic factors in chorea that we found. According to him it supplies an adequate amount of calcium, produces a useful sedative effect on the brain and combats the rheumatic element if given in sufficient doses, readily dissolving in water and forming a neutral solution suitable for administration by vein or subcutaneously as well as by mouth. By crystallization from a solution of calcium chlorid, a form of calcium acetylsalicylic acid has been obtained with a stability approximately equal to that of the parent acetylsalicylic acid itself. The author's 19 patients were kept in bed. A light, mixed diet was given. The only drug employed except laxatives was calcium acetylsalicylic acid, dissolved in water and administered by mouth. The average daily dose varied up to gr. xlv for a child aged 12 years. The rapidity of response did not vary accurately with the original severity of the choreic movements, as mild cases sometimes proved to be more resistant than severe ones. The attack was not registered as over until the condition had so far improved that an average medical man would have had difficulty in diagnosing the case as one of chorea. Spontaneous movements would have stopped. Voluntary movements were of average accuracy, and the patient could sustain a steady grip of the hand for a minute or so without fluctuation. The average time taken to control chorea was 17 days and the limits were 7 to 46 days. The drug diminished the discomforts of the patients at all stages of the treatment, and did not produce any mental depression, undue drowsiness or digestive derangement. There were no relapses or secondary exhaustion when the drug was finally withdrawn.

Charney[8] and Williams[9] treated 2 and 4 cases respectively with J. C. Small's antiserum for Streptococcus cardio-arthritidis. Small had reported favorable results with antiserum and vaccine and described a skin test for susceptibility. His articles on specificity and his results were convincing enough to induce many clinicians to use this serum, but few have reported their results. Swift has stated that this serum causes a non-specific reaction, similar to that obtained with any anti-

streptococcic serum. Charney, feeling that reports of unfavorable results are as essential as are favorable reports, described 2 cases of chorea, treated with the serum, one with apparently no result and the other with a reaction that appears to have led to the death of the patient. The cases were chosen as illustrating extremes of severity of the disease and because of the difference in the results.

"The Nirvanol Therapy of Chorea" was the subject of a paper by deRudder.[10] Nirvanol is a phenyl-ethyl-hydantoin that was introduced originally as a new sedative and was widely used as such. In 1919 Roeder reported good results obtained with nirvanol in the treatment of chorea minor, but observed that during the nirvanol medication a drug exanthem developed. Rietschel reported in 1920 on the basis of a study of cases that this drug exanthem was essential for the production of the therapeutic effect of nirvanol. Because of its unpleasant side effects the drug is no longer used as a sedative, but it is employed largely in the treatment of chorea. Nirvanol is indicated only in the treatment of the severest cases of chorea and its complications must be considered. It must be emphasized that the nirvanol treatment must not be looked upon as indifferent. In severe cases the use of this drug is definitely indicated. Because of the risks associated with the treatment, nirvanol medication is employed largely only in the hospital where the patient can be carefully watched by a competent physician. The effect of the drug is based on the appearance of the exanthem. In order to produce this a daily administration of the drug is necessary. If no reaction takes place after 14 days the use of the drug must be discarded since an exanthem could no longer be expected. The dose of the drug is generally 0.3 gm. per day and in older children it is occasionally used in doses of 0.6 gm. per day. This dose must under no conditions be exceeded. During the medication strict bed rest must be maintained. The "nirvanol disease" appears between the 6th and the 14th days. Around this time there develops a morbilliform exanthem frequently associated with fever. The degree of intensity of the exanthem varies. Occasionally there is also observed a slight irritation of the conjunctivæ. In rare cases the reaction may be severe. Rusleer observed a case with a severe recurrent exanthem, severe stomatitis, balanitis, and a very high fever. Joloicz observed a case of transitory intestinal paralysis with a high degree of tympanites following the use of excessive doses. These severe although rare cases show the great necessity of care when this treatment is employed. Its use is justified by the fact that chorea itself may result fatally. The success of the therapy and the appearance of the reaction is lightning-like and more or less certain. Of interest is the fact that occasionally shortly before the appearance of the reaction, a slight aggravation of the choreic twitchings may be observed. Regarding the biologic character of the nirvanol disease, it may be stated that it has some resemblance to an anaphylactic reaction. The incubation time of from 9 to 12 days may be considered as the time necessary for the development of amboceptors until then absent from the body. The clinical picture is identical with that of serum disease. There frequently develops an eosinophilia of a considerable degree. The metabolic-chemical changes are similar to those observed in serum disease. Shortly before the appearance of the reaction there develops an alka-

lotic change in the organs, a "pre-anaphylactic tetany" similar to that observed in serum disease. There also develops a galvanic hyperirritability of the peripheral nerves. As the exanthem develops there occurs a change in the metabolism in the direction of acidosis, and it seems that this type of "metabolic shock" is the most important factor in the nirvanol therapy.

Dennett,[11] who studied 93 cases of chorea treated with nirvanol, said, "One has to use the drug with caution—one must have brains as well as the drug." Marick,[12] presenting his experience in some 60 cases, feels that the nirvanol treatment of the chorea patient at home is safe and practical. This is contrary to the opinion of practically every other observer. Call[13] had 26 cases in his series. Silber and Epstein[14] studied 28 cases of chorea treated with nirvanol.

Freire[15] claimed that constant and excellent results were produced with febrifacient injections of Sufrogel. The production of fever by a serologic product was described first by Sutton.[16] Her investigations were based on the hypothesis that the fever is the effective factor in the treatment which she described. She fully realized that this point was not proved and that other immunologic factors may be operative; but support is lent to this hypothesis by the fact that fever is common both to intoxication with drugs such as phenobarbital and phenyl-ethyl-hydantoin, which may have a beneficial effect on the chorea, and to foreign protein therapy. In order to investigate this question, typhoid vaccine was given to most of the choreic children at Bellevue Hospital during parts of 1929 and 1930. This vaccine was chosen as a simple and safe means of producing fever. The object was to obtain fever for several days in succession. With plain typhoid vaccine, fever was not produced if the injections were given at intervals of less than 5 to 7 days, and not every case responded with high fever. Possibly if larger doses had been given, more sharp reactions would have occurred. However, enough cases showed marked improvement following a sharp febrile reaction to encourage a continuation of this line of treatment. In the fall of 1930 typhoid-paratyphoid vaccine was tried. This vaccine when given intravenously invariably produced a sharp febrile reaction, even when given every day. Up to the time of her report in May, 1931, Sutton had treated 24 cases of chorea with intravenous injections of this vaccine with encouraging results. It is possible that some other more satisfactory way of producing fever may be found, but this method is simple, safe and cheap. The progress of the chorea was used as a guide for the continuation of the treatment. Most cases seemed to require a febrile period of about a week, while others needed more, depending chiefly on the severity and duration of the attack. Except for rest in bed and general nursing care, no other treatment was employed in this series. When possible, the children were kept in small rooms off the ward; but a number were treated in cubicles in the ward with no attempt at special isolation and quiet. Codein was given in some cases for severe headache during the reaction. It is important to note that acetylsalicylic acid is contraindicated, since it reduces the temperature. The injection was usually given in the afternoon, so that the child would not miss his dinner. The reaction was over in time for him to have an undisturbed night's sleep. The effect of the fever on

the chorea was usually immediate. After the febrile reaction was over, the movement was noted after each reaction. Most of the children lost weight during the period of treatment and sometimes seemed worn out after it. For this reason they were kept in bed for a week after the treatment was stopped, in order that they might regain their strength before being allowed any activity. They were kept in the hospital for another week of observation while up and about the ward. High-caloric diets were given with extra milk, cod-liver oil and iron tonics when indicated. A few were given transfusions of whole blood for moderate secondary anemia. Such measures were designed to hasten convalescence. Occupational therapy was found to be helpful in keeping the children busy and happy. It was particularly helpful where there was incoördination due to muscular weakness, which often persists after the real chorea is over.

Dennett (*loc. cit.*), however, found that the reactions to typhoid vaccine in some patients were too severe to warrant its use, and he does not allow its use on his wards, preferring nirvanol in the treatment of this disease. Cheetham[17] presented several examples from his series of cases and concluded that the treatment of chorea by artificial pyrexia shortens the duration of the choreic movements, but does not prevent recurrences and does not appear to have a beneficial action on rheumatic carditis. In view of these conclusions it is clear that the method requires exhaustive trial before it can be generally adopted. Its grave danger lies in the tendency to produce a false impression of cure by abolishing the movements, which in themselves are merely a symptom, when serious changes may be occurring in the heart. A child with acute rheumatism should not be allowed out of bed as soon as the joint swellings have subsided under the influence of salicylates. In the same way it is undesirable to allow a child out of bed after the onset of an attack of chorea unless it can be conclusively proved that the treatment which cut short the choreic movements also cut short any accompanying carditis. When these facts are borne in mind it is clear that artificial pyrexia has a very limited place in the treatment of chorea according to the contention of Cheetham.

Walker,[18] Bateman[19] and Hoverson[20] are among those who have published favorable reports. Walker believed that since the good effects of the treatment depend on the fever produced, vaccine treatment would seem to have distinct advantages over phenyl-ethyl-hydantoin for all cases can be made to react immediately without waiting for a period of days for the toxic symptoms to develop, there are no complications, the results are as good or better and the amount necessary to obtain a satisfactory febrile reaction is under perfect control. Bateman said, "Most patients show a marked improvement after two or three treatments, and are usually free from choreic movements in a week." As might be expected the milder cases improve more quickly than the severe ones. Patients with a long history of chorea before admission to the hospital may be slow in their response to treatment, and it should be remembered that in those patients habit movements may be superimposed upon those that are essentially of choreic origin. At the end of the fever treatments the patients should be kept in bed for a few days and are then allowed up for a week before discharge

from the hospital. The usual length of time in the hospital is 3 weeks. This compares very favorably with the 7 weeks which most other methods require. Mention may be made of those cases of chorea which on admission to the hospital show a cardiac murmur of rheumatic origin. This need not be regarded as a contraindication to treatment, unless it is thought that the circulatory system cannot support the effects of a high fever. Walker feels that the treatment has proved satisfactory. It has considerably shortened the duration of the stay in the hospital and it is not accompanied, so far as is known at present, by complications. The patient's discomfort attendant upon the treatment is much less than might be expected, and it is probably preferable to the weeks in bed and the long continuance of choreiform movements associated with the other methods. Hoverson reported a series of 6 cases, 4 suffering from the Huntington's type of chorea and 2 cases of Sydenham's chorea that were treated by fever therapy which was induced by the intravenous injection of typhoid vaccine. In the cases of Sydenham's chorea, there was a complete recovery from the chorea. Regarding the more chronic chorea, 2 patients showed a recovery, 1 a temporary improvement, and 1 no change. He felt that fever therapy is of definite value both for the acute and the chronic forms of chorea.

Montfort,[21] in an attempt to clarify the present status of the treatment of chorea, made a comparative study of 49 patients, 24 of whom were treated with phenyl-ethyl-hydantoin and 25 with typhoid-paratyphoid vaccine. He found that there were spectacular benefits from phenyl-ethyl-hydantoin in some cases, but in the majority of cases the average duration of the disease was 24 days; in 8 cases the condition was unimproved; in 1 case the drug caused a fatality. There is justification, therefore, for characterizing this method as of questionable value. The results of treatment with typhoid-paratyphoid vaccine showed that this form of therapy was not dangerous, but that it produced obvious discomforts such as chills and fever during the febrile period. However, the duration of treatment with this method was shorter by 8 days than that with phenyl-ethyl-hydantoin. There were no recurrences of chorea in the patients treated with the typhoid-paratyphoid vaccine who were followed for one year, and it was noted that carditis, the most dangerous sequel of chorea, did not occur in those treated with this preparation during this period of observation. It is, of course, too soon to make any sweeping conclusions as to the advantages of treatment with typhoid-paratyphoid vaccine, but it would seem that this ought to be the treatment of choice. In Montfort's series of cases the time required to arrest the symptoms was from 2 to 3 days longer than in the patients in Sutton's series. Speculating as to the factor responsible for the improvement in these cases, one is impressed by the chemical changes taking place during the febrile period when the typhoid-paratyphoid vaccine is introduced. There was noted a change in the acid-base equilibrium. There was invariably a low carbon dioxid content of the blood during the prolonged fever, with a low level for chlorids, a moderate raising of the calcium level and a lowering of the phosphorus level. It was observed in 3 cases that the pH of the blood was slightly increased coincidentally with

the lowering of the carbon dioxid content. The question arises whether this sudden shift in the acid-base is operative in the improvement, or whether the improvement is due to the increase in calcium during the febrile period. Although there is a lowering of the carbon dioxid volume per cent and the chlorid level, there is an increase in pH. The bases are not lost, but are bound to the proteins, owing to the increase in pH. There is probably a sudden shift to alkalinity. Bischoff, Ullman, Hill and Long, discussing hyperthermia, confirmed the hypothesis that of all the changes taking place in the chemistry of the body following a gradual moderate rise in body temperature, the one of fundamental importance is the loss of CO_2. This was pointed out previously by others. The data of this series illustrated this point very strikingly. The one effect which was the same in all of the experiments was the rise in the blood pH. This, in connection with other data, showed conclusively a lowered carbon dioxid tension of the blood. The other changes, which in some instances did not follow, were a result of the lowering of the carbon dioxid tension. Thus, the pH of the urine remained unchanged or decreased, the calcium was unchanged or increased, and the hemoglobin was more or less highly oxygenated. The change in the total CO_2 content of the blood was readily accounted for by the shift of the base to the blood protein due to the increase in pH. Since the alkali reserve of the blood remained the same or increased slightly, and since the pH of the urine as excreted was not more alkaline than the blood there is little reason for believing that the body was attempting to compensate for the lowered carbon dioxid tension by lowering the alkali reserve. Diminution of the blood pressure was also noted during the febrile period. The pulse pressure fell disproportionately more than the systolic pressure. Of the entire series, 17 patients treated with phenyl-ethyl-hydantoin and typhoid-paratyphoid vaccine showed evidence of carditis on admission; 23 of the entire series had had their tonsils removed, and 8 showed roentgenographic evidence of sinus and antral involvement. All of the patients treated with typhoid-paratyphoid vaccine gave a positive Widal reaction in all dilutions during their stay in the hospital. From these observations it may be concluded that typhoid-paratyphoid vaccine proved of greater value in the treatment of chorea than phenyl-ethyl-hydantoin because of its harmlessness, the shorter time required for cure, the probable arrest of recurrences, the ease of administration, the significant lack of sequelæ and the occurrence of chemical changes during the febrile period.

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PHYSIOLOGY

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An Analysis of the Spectra of Hemoglobin Derivatives.—DAVID L. DRABKIN (Laboratory of Physiological Chemistry, University of Pennsylvania). A study of the absorption spectra in both the visible and ultra-violet regions of several hemoglobin derivatives has led to an analysis which heretofore has been applied only to the absorption spectra of very simple substances.

The complex absorption curves may be considered to represent summations of a number of individual bands. All the derivatives studied —oxyhemoglobin, carboxyhemoglobin, cyanhemoglobin and two forms of methemoglobin—have certain bands in common. The position of the peaks of these bands may be expressed by $n = \frac{\nu \times 10^{-2}}{60}$, where n represents a simple integer. In the regions of the spectra studied the values of n which have been obtained are 3, 4, 5, 6, and 7. These five bands therefore belong to a single series, the members of which are at equal frequency differences from each other. Such bands are probably produced by the same influence in the molecule, and are deduced to represent the general structure of hemoglobin.

The so-called α-bands of oxyhemoglobin and carboxyhemoglobin do not belong to the above series and probably represent the union of hemoglobin with a gas. Such an analysis also suggests that hemoglobin may have absorption in the infra-red, where the first two members of the $\frac{\nu \times 10^{-2}}{60}$ series may possibly be demonstrated.

Observations on the Effects of an Arteriovenous Fistula on the Human Circulation.—L. B. LAPLACE (Laboratory of Physiology, University of Pennsylvania). A case is described which presented a traumatic fistula between the left femoral artery and vein. The fistula had caused an enormous cardiac enlargement and advanced congestive failure. The cardiac output was decreased 20% on digital compression of the fistula and 24% after operation. The change in minute volume de-

pended chiefly on slowing of the heart rate rather than on change in stroke volume. Slowing of the heart rate on compression of the fistula was not directly proportional to the associated elevation of arterial pressure, indicating that other factors must be involved in the bradycardiac reaction. Despite the presence of the open fistula the arterial blood pressure, although low, was maintained within normal physiological limits. The skin temperature was elevated in both legs on compression of the fistula, indicating an increase in capillary blood flow when the leak was blocked. Following treatment the heart size returned to normal indicating that the enlargement was due to dilatation rather than hypertrophy. The dilatation appeared to depend, as Lewis and Drury believe, on a disproportion between the work of the heart and the coronary blood flow. Fluoroscopic examination demonstrated a prompt diminution in pulmonary blood volume on compression of the fistula. The effect of the fistula on respiration, venous pressure, oxygen consumption, pulse wave velocity, and the electrocardiogram are also described.

The Effects of Prolonged Exercise on the Weights of the Organs of the Albino Rat.—HENRY H. DONALDSON (The Wistar Institute, University of Pennsylvania). The brain of the captive albino rat weighs 10 to 12% less than that of the wild Norway, from which it is derived. Continued exercise in the drum cage increased the brain weight of the albino by about 2%. When this form of exercise was continued for seven generations, the gain in the last generation was again about 2%. This modification is, therefore, not inherited.

Starting at 57 and ending at 182 days of age, the effect of such exercise on 14 other organs was determined on 26 males and 26 females. Each group ran 500 miles in 125 days. In the females all the organs and in the males all except the thyroid and thymus show increased weights. The increases are substantial except for the musculature, brain and cord. The final body weights were below those of the controls despite the fact that the male tests gained 5.9 gm. and the female tests 3.5 gm. from their heavier organs. The diminished body weights are credited to a loss of fat by the tests.

When rats are exercised for 90 days and then rested for 125 days, the organ weights of the tests are much nearer those of the controls. The deviations, therefore, do not persist. Exercise as here used produces accelerated growth; but during the subsequent resting period the organs of the tests grow less rapidly than those of the controls. It seems probable that a similar type of exercise would produce like changes in the organs of man.

The Effect of Oxygen in the Prevention of the Liver Necrosis Produced by Volatile Anesthetics. — S. GOLDSCHMIDT, I. S. RAVDIN and BALDUIN LUCKÉ (Laboratories of Physiology, Research Surgery and Pathology, University of Pennsylvania). A comparison has been made of the relative incidence of liver necrosis in dogs anesthetized in a semiclosed system when the anesthetic was volatilized with air and when it was volatilized with oxygen. The data show that the use

of oxygen with either divinyl ether or chloroform is a potent factor in the reduction of postanesthetic liver necrosis.

When divinyl ether was used as the anesthetic by any method, liver necrosis was not observed with any degree of regularity until the anesthesia was maintained for a 3-hour period. The incidence of postanesthetic necrosis after 3 hours of anesthesia in a semi-closed system was nearly twice as high when the anesthetic was volatilized with air as with oxygen.

Chloroform anesthesia on the other hand resulted in a high incidence of liver necrosis in dogs after 1 hour of anesthesia. The incidence of liver necrosis following 1 hour of chloroform anesthesia in a semi-closed system was approximately ten times as great when the anesthetic was volatilized with air as with oxygen.

Liver degeneration has been produced in the dog following 3 hours of ether anesthesia when the anesthetic was volatilized with less than atmospheric pressure of oxygen, *i. e.*, oxygen 15% and nitrogen 85%.

Data demonstrating the effciency of oxygen during anesthesia will be presented and the general implications of our findings will be discussed.

Correction.

In the article by L. F. Craver in the November, 1934, issue of this journal, on "Five-year Survival in Hodgkin's Disease," the percentage figure of survival of proven cases in the summary (p. 612), should be 12% and not 16.8%.

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